# Organometallic Methods for Forming and Cleaving Carbon-Carbon Bonds

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# Organometallic Methods for Forming and Cleaving Carbon-Carbon Bonds

Ph.D. Thesis

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## Acknowledgement

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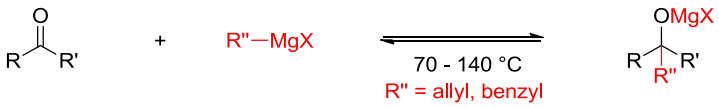
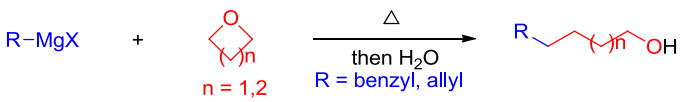
## Abstract

The retro-Grignard addition reaction has been revisited and the benzyl addition reaction was found to be a reversible transformation by using crossover experiments. The retro benzyl addition reaction was shown by the addition of benzylmagnesium chloride to di-*t*-butyl ketone followed by exchange of both the benzyl and the ketone moiety with another substrate. Similar experiments were performed with phenylmagnesium bromide and *t*-butylmagnesium chloride, but in these two cases the Grignard addition reaction did not show any sign of a reverse transformation.

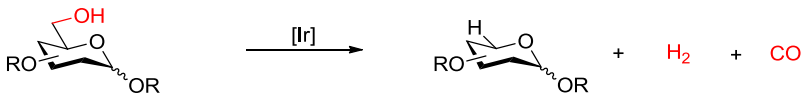



The ring-opening of cyclic ethers with concomitant C-C bond formation was studied with a number of Grignard reagents. The transformation was performed in a sealed vial by heating to about 160 °C in an aluminum block or at 180 °C in a microwave oven. Good yields of the product alcohols were obtained with allyl- and benzylmagnesium halides when the ether was tetrahydrofuran or 3,3-dimethyloxetane. Lower yields were obtained with substituted tetrahydrofurans while no ring-opening was observed with tetrahydropyran. Only highly reactive allyl- and benzylmagnesium halides participated in the transformation while no reaction occurred with other alkylmagnesium halides.

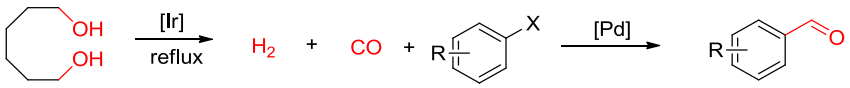



Carbohydrates with protecting groups on all alcohol groups except the primary alcohol were prepared and subjected to the iridium catalyzed dehydrogenative decarbonylation reaction where primary alcohols are converted into the corresponding one carbon shorter products. Modest conversions were obtained when isopropylidene- or cyclohexylidene ketals were used as protecting groups, but the conversion rate was slow. Low conversion was obtained when the alcohols were

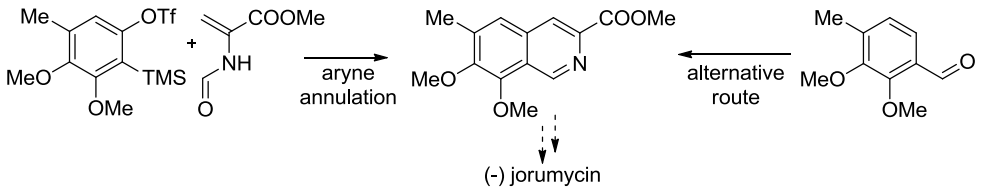
protected by benzyl groups and the carbohydrates were unstable at the required temperatures.




The syngas evolved from the iridium catalyzed dehydrogenative decarbonylation reaction was consumed in a palladium catalyzed reductive carbonylation reaction in a two-chamber system setup. Carbohydrates were not found to be a viable syngas source because they did not liberate sufficient syngas. Carbohydrates were attached to several lipophilic anchors and performing the dehydrogenative decarbonylation with the anchor monools proceeded well, while the corresponding anchor triols were unstable at the elevated temperatures. Of the simple primary alcohols investigated, 2-(2-naphthyl)ethanol, hexane-1,6-diol and dodecane-1,12-diol were found to be the most promising syngas sources. A substrate scope for the reductive carbonylation of aryl bromides is currently under development by using hexane-1,6-diol as a syngas source.

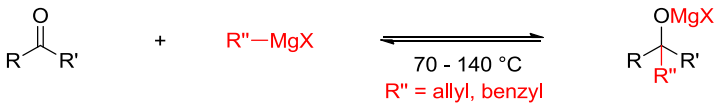



The synthesis of the anticancer antibiotic tetrahydroisoquinoline alkaloid jorumycin progressed via a route consisting of a crucial aryne annulation step where an isoquinoline scaffold was prepared. The aryne annulation step was problematic and after several attempted modifications to the formerly optimized procedure; no further improvement was obtained. Gratifyingly, an alternative route was found for the formation of the isoquinoline scaffold and further optimization of this route is needed.

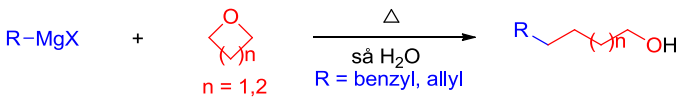


## Resumé

Retrogrignardadditionsreaktionen er blevet revurderet og benzyladditionsreaktionen er fundet til at være en reversibel transformation ved at bruge krydssubstrateksperimenter. Retrobenzylreaktionen blev vist ved additionen af benzylmagnesiumklorid til di-*t*-butylketon og derefter udveksling af både benzyl- og keton-delen med et andet substrat. Lignende eksperimenter blev udført med phenylmagnesiumbromid og *t*-butylmagnesiumklorid, men i disse to tilfælde viste Grignardadditionsreaktionen ingen tegn på at være en reversibel transformation.



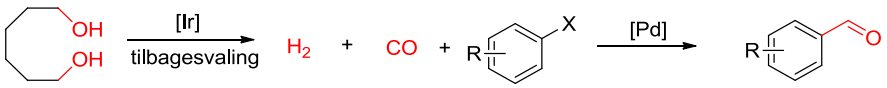

Ringåbning af cykliske ethere med simultan C-C bindings dannelse er blevet studeret med en række Grignardreagenser. Omdannelsen blev udført i en lukket vial med opvarming til omkring 160 °C i en aluminiumsblok eller til 180 °C i en mikrobølgeovn. Gode udbytter af alkoholproducterne blev opnået med allyl- og benzyl-magnesiumhalider, når etheren var tetrahydrofuran eller 3,3-dimethyloxetan. Lavere udbytter blev opnået med substituerede tetrahydrofuraner, mens der ikke blev observeret ringåbning med tetrahydropyran. Kun meget reaktive allyl- og benzyl-grignardreagenser blev omdannet, imens der ikke skete nogen reaktion med andre alkylmagnesiumhalider.



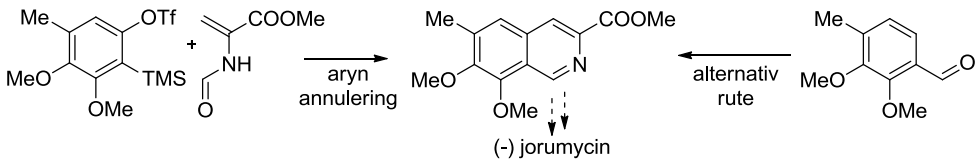

Kulhydrater med beskyttelsesgrupper på alle alkoholgrupper bortset fra den primære alkohol blev fremstillet og udsat for den iridiumkatalyseret dehydrogenerende decarbonylering hvor primære alkoholer konverteres til det tilsvarende et-carbon-mindre produkt. Moderat omdannelse var opnået når isopropyliden- eller cyklohexyliden-ketaler var brugt som beskyttelsesgrupper men omdannelseshastigheden var langsom. Lav omdannelse var opnået når alkoholerne

var beskyttet med benzylgrupper og disse kulhydrater dekomponerede under reaktionsbetingelserne.


Syngassen der blev udviklet fra den iridiumkatalyserede dehydrogenerende decarbonyleringsreaktion blev forbrugt i en palladiumkatalyseret reduktiv carbonyleringsreaktion i et tokammersystem. Kulhydrater blev ikke fundet til at være brugbare syngaskilder, fordi de ikke frigav tilstrækkelige mængder af syngas. Kulhydrater blev vedhæftet flere lipofile ankere og udførelsen af den dehydrogenerende decarbonyleringsreaktion på monool ankere fungerede udmærket, mens de tilsvarende anker trioler var ustabile ved de forhøjede temperaturer, som reaktionen kræver. Af de testede enkle primære alkoholer blev 2-(2-naphthyl)ethanol, hexan-1,6-diol og dodecan-1,12-diol fundet til at være de mest lovende syngaskilder. Et substratstudie omkring den reduktive carbonylering af arylbromider er i øjeblikket ved at blevet udført ved at bruge hexan-1,6-diol som syngaskilde.




Syntesen af anticancer tetrahydroisoquinolinalkaloidet jorumycin udviklede sig videre frem via en rute, der omfattede et vigtigt arynannuleringstrin, hvor et isoquinolinstof blev fremstillet. Arynannuleringstrinnet var tidligere fundet problematisk og selv efter adskillige afprøvede modifikationer af fremgangsmåden blev der ikke fundet yderligere forbedringer i denne reaktion. Glædeligvis blev der fundet en alternativ rute til isoquinolinstoffet, hvor yderligere er optimering af ruten dog er nødvendig.



## Abbreviations

Ac = acetyl

AIBN = azobisisobutyronitrile

All = allyl

aq. = aqueous

BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

BIPHEP = 2,2'-Bis(diphenylphosphino)-1,1'-biphenyl

BMI = 1-Butyl-3-methylimidazolium

Bn = benzyl

bp = boiling point

cod = cycloocta-1,5-diene

coe = cyclooctene

Conv. = Conversion

Cy = cyclohexyl

d = day(s) (in tables)

d = doublet (in compound data)

DMA = dimethylacetamide

DME = 1,2-dimethoxyethane

DPEN = diphenylethylenediamine

dppe = 1,2-Bis(diphenylphosphino)ethane

dppp = 1,3-bis(diphenylphosphino)propane

equiv. = equivalent(s)

Et = ethyl

h = hour(s)

*i*Pr = isopropyl, propan-2-yl

HFIP = hexafluoroisopropanol

$k_1$ = first-order rate constant

Me = methyl

min = minute(s)

MHF = 2-methyltetrahydrofuran

*n*Bu = normal butyl

nu. = nucleophile

ox. = oxidation

p = pressure

Ph = phenyl

PPA = polyphosporic acid

R = right (latin: Rectus, in stereochemistry)

rac = racemate

red. = reduction

SET = single-electron transfer

t = temperature

T = time

TBAF = tetra-*n*-butylammonium fluoride

TBAT = tetra-*n*-butylammonium difluorotriphenylsilicate

*t*Bu, *t*-butyl = *tert*-butyl, tertiary butyl

Tf = trifluoromethanesulphonyl

TFA = trifluoroacetic acid

TFAA = trifluoroacetic anhydride

THF = tetrahydrofuran

THP = tetrahydropyran

THIQ = tetrahydroisoquinoline

TMEDA = tetramethylethyldiamine

$To^M$ = tris(4,4-dimethyl-2-oxazolinyl)phenylborate)

Tr = Trityl, triphenylmethyl

triphos = bis(2-diphenylphosphinoethyl)phenylphosphine

UHPLC = ultra high performance liquid chromatography

V = volume

# Table of Contents

# Chapter 1: Introduction

## 1.1 Organometallic chemistry

Organic chemistry mainly focuses on compounds containing bonds between carbon and carbon as well as carbon and hydrogen, nitrogen, oxygen, phosphor, sulfur and halides as opposed to inorganic chemistry that mainly focuses on the study of non-carbon based compounds. Organometallic chemistry is an overlapping field of inorganic chemistry and organic chemistry and is the study of compounds containing bonds between a metal and carbon. Metals cover most of the periodic table of elements and the metals are highlighted in blue in Figure 1. Transition metals are defined by IUPAC as: "an element whose atom has an incomplete d sub-shell, or which can give rise to cations with an incomplete d sub-shell".[1] This is the case for any elements in the *d*-block of the periodic table and therefore includes the groups 3-12 which all have between 1 and 10 *d* electrons.

Organometallic compounds can be distinguished from other metallic compounds by the prefix "organo-" and the suffix can specify the metal which bonds to the carbon. For instance, organolithium compounds like *n*-butyllithium and organomagnesium compounds like *n*-butylmagnesium bromide have the same "organo" part but differentiate in the metal.

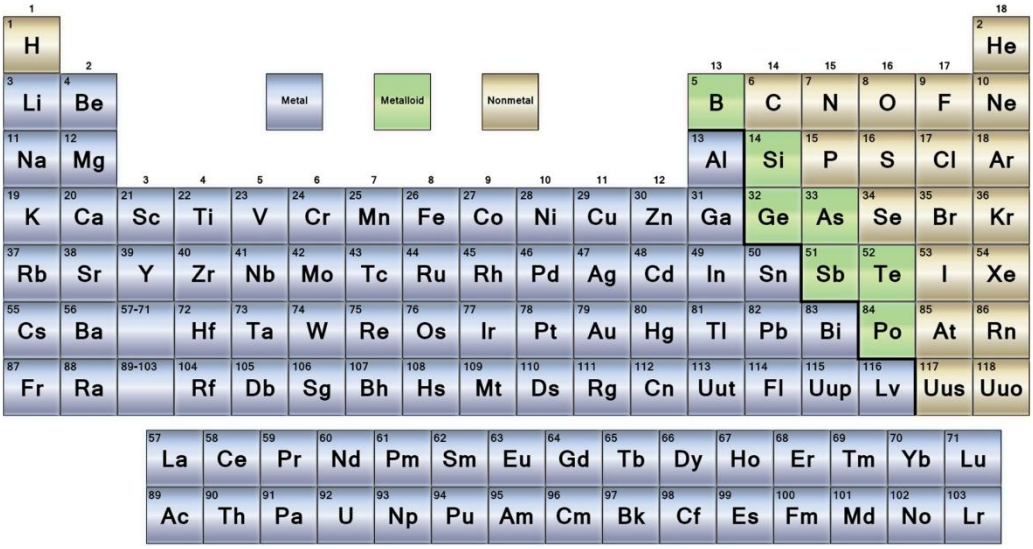



**Figure 1 - Periodic table of elements**

### 1.1.1 History of organometallic chemistry

The historic timeline of organometallic chemistry spans over 250 years of discoveries. One of the first known organometallic compounds have been reported by Louis Claude Cadet de Gassicourt in the 18 century where he have isolated cacodyl - an arsenic compound.[2] Charles Friedel and James Crafts discovered the Friedel-Crafts reaction in 1877 where aluminum chloride catalyzes the alkylation or acylation of various aromatic compounds.[3] The Grignard reaction is the formation of organomagnesium halides (Grignard reagents) from organic halides and the Grignard addition reaction is the reaction with the formed Grignard reagent to a ketone. The first known example of a Grignard addition reaction have been discovered by Barbier in 1899 and he assigned his student, Victor Grignard, to unravel the mechanism of his results.[4–6] Victor Grignard have been awarded the Nobel Prize in Chemistry for his work along with Paul Sabatier who have received the award for his work with improving the hydrogenation of organic species in the presence of metals.[7]

Homogeneous transition-metal catalysis have revolutionized the field of organometallic chemistry within the last 50 years and the revolution began with the

Mizoroki-Heck reactions as the first example of a palladium catalyzed carbon-carbon bond forming reaction. Independently, Mizoroki and coworkers have reported the cross-coupling of iodobenzene with acrylate to give cinnamate, while Heck and Nolley have reported the cross-coupling between iodobenzene and styrene to form stilbene by organopalladium catalysis.[8–10] In 2010, Richard Heck have been awarded the Nobel Prize in Chemistry for his pioneering discoveries along with Ei-ichi Negishi and Akira Suzuki, who also have contributed with organopalladium catalyzed reactions.

Oxidation of organic compound is an essential synthetic tool in organic synthesis and in the oxidations of alcohols with $H_2O_2$ or $O_2$, a transition metal catalyst such as palladium, copper or ruthenium have been applied widely.[11] Traditionally, the use of iridium as a catalyst, has not received the same amount of attention and is most likely a consequence of the stability of iridium complexes which often are least effective when comparing with the other group 9 metal complexes, rhodium and cobalt.[12] However, since Crabtree *et al.* have reported a dehydrogenation of alkanes using an iridium catalyst, the research in using iridium catalysts have made tremendous progress.[13,14]

### 1.1.2 Structure and properties of organometallic compounds[15]

The carbon-metal bonds are often an intermediate between being an ionic bond and a covalent bond. Mostly, ionic bonds are present when the metal atom is very electropositive, as observed for most group 1 and 2 metals and the ionic character is also observed when the ligand is a stable carbanion. Therefore the carbon-magnesium bonds usually have a more ionic character as compared to the transition metal-carbon bonds. The intermediate bond characteristics that exist in the carbon-metal bonds of organometallic compound are really important as they are stable in solutions and therefore are able to undergo reactions.

Organometallic chemistry consists of a vast array of metals, oxidation states and ligands and therefore general principles exist to aid in the prediction of the reactivity and stability of the organometallic complexes. Electron counting provides a valuable tool and the count of valence electrons includes metal group, ligand donation and

charges. As predicted by the 18-electron rule used in transition metal electron counting, stable, diamagnetic, mononuclear organotransition metal complexes almost always contain 18 or fewer valence electrons. These 18 electrons can be localized in the nine valence orbitals: one *s*-orbital, three *p*-orbitals and five *d*-orbitals, although the *p*-orbitals often do not participate significantly in the metal-ligand bonding.

Transition metal complexes can adopt many geometries and the geometry of a certain complex can usually be predicted with the number of valence electrons and the formal *d*-electron configuration. The actual geometry originates from steric effects and electron effects and frequently the two effects have different favored geometries. Often, the electronic effects will override the steric effects. Overall, the preference for a specific geometry is the result of its total energy of all its filled valence orbitals is being lower than the total energy of the other possible geometries.

### 1.1.3 Organometallic transformations[15]

Due to the properties of the organotransition metallic compounds, they can undergo several reactions useful in synthesis. Some of the most important are listed here and depicted in Figure 2.

- **Ligand substitution** is a reaction where a free ligand replaces a coordinated ligand on the metal. The reaction can occur by an initial dissociation of the free ligand, by association of the coordinated ligand or by interchange where the association and dissociation occur simultaneously.
- **Oxidative addition** increases the formal oxidation state of the metal by the addition of new metal ligand bonds while bonds in organic or main group reagents are cleaved. An example outside the transition metal chemistry is the formation of Grignard reagents where magnesium (0) is oxidized to magnesium (II). The oxidative addition can occur with both polar and non-polar reagents.
- **Reductive elimination** is the reverse reaction of the oxidative addition reaction. This step is often the product-forming step and the reaction forms products by coupling of two covalent ligands at either a single metal center or two different metal centers.

- **Migratory insertion** is where an unsaturated ligand combines with an adjacent coordinating ligand and is followed by the binding of a Lewis base to the vacant site. The unsaturated ligand can be carbon monoxide, carbon dioxide, an olefin, an alkyne, a ketone or related species.
- The **elimination** reaction often occurs in the reverse direction of the migratory insertion. The most common types of elimination reactions are the β-hydride eliminations and the decarbonylation of aldehydes. β-Eliminations are not restricted to substrates with a β-hydrogen as also alkyl, aryl alkoxide and halide groups undergo the transformation.
- **Transmetalation** involves the transfer of ligands from one metal to another and this reaction is often an irreversible process due to themodynamic and kinetic reasons. Transmetalation is often used in cross-coupling reactions where the most useful catalyst tends to be palladium.[16] For instance, the transmetalation is an essential transformation in the Kumada coupling where organomagnesium halides are coupled with organohalides with palladium or nickel catalysis.[17–20]

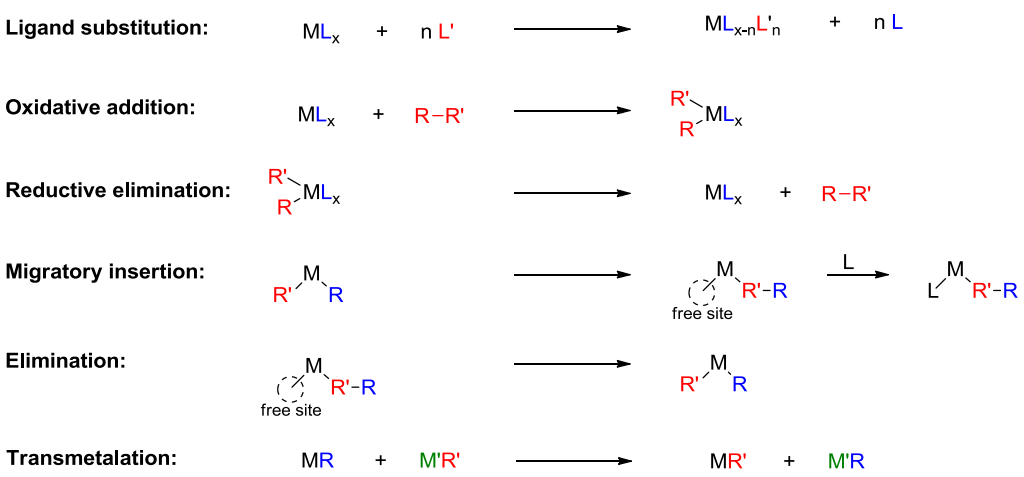



**Figure 2 - Organometallic transformations**

## 1.2 Catalysis[15]

In the Grignard addition reaction, a stoichiometric amount of magnesium is necessary for performing the transformation. This is acceptable for magnesium in an economical perspective as this metal is readily available and an abundant element in the Earth's crust. However, this is not the case for most transition metals and therefore catalytic reactions are necessary for the metals to be employed industrially. Furthermore, catalysis provides a method for making a process more "green" and therefore more environmentally friendly since less waste compounds are being produced.

A catalyst is defined as a substance that increases the rate of a transformation without itself being consumed. There are several types of catalytic systems in modern chemistry: enzymatic catalysis, organocatalysis[21], electrocatalysis[22] and organometallic catalysis. The catalysis can occur heterogeneously, where the catalyst is not in the same phase as the substrates, as opposed to homogeneously where the catalyst is in the same phase as the substrates.

A simple comparison of an uncatalyzed process *versus* a catalyzed process is shown in the energy diagram in Figure 3. The Gibbs free energy of a transformation is unchanged by the addition of a catalyst but the energy of the transition state is lowered. Therefore the kinetic energies are affected by a catalyst but not the thermodynamic energies of a reaction.

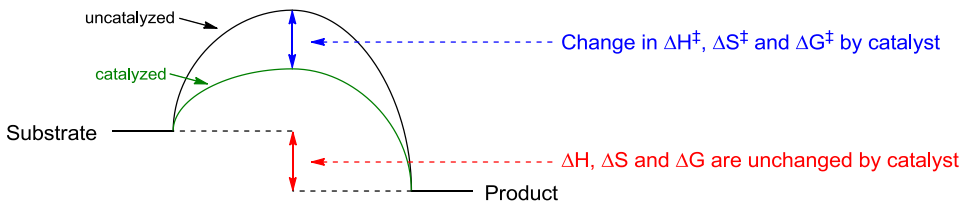



**Figure 3 - Energetic effect of catalysis**

The catalyst can lower the energy of the transitions state by stabilizing this state or the catalyst can create a completely new reaction pathway compared to the uncatalyzed reaction.

The catalytic cycle is the combination of transformations that occurs in a catalytic reaction and therefore the initial form of the catalyst is being regenerated (Figure 4). The substrate enters the catalytic cycle at some point and the product is being liberated from the cycle at a later step. Often in organometallic chemistry, the active catalyst is being generated *in situ* from catalyst precursors by attachment of ligands. Furthermore, when the catalytically active species is transformed into a species that exist out of the catalytic cycle the catalyst may be deactivated. The deactivation can occur reversibly, where the inactive species is returning into the cycle, or irreversibly where the cycle is stopped.

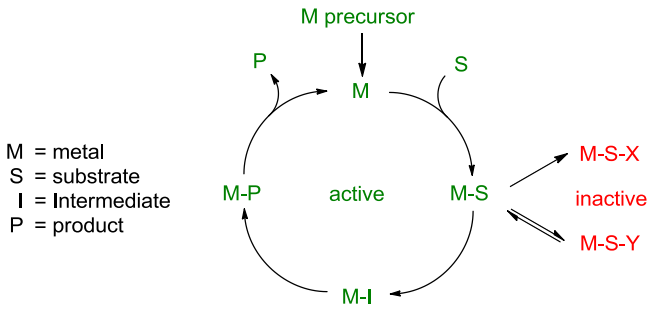



**Figure 4 - Catalytic cycle**

## 1.3 Project outline

In the following chapters, a scientific background, results, discussion and experimental part of the work performed are described. Chapter 2 to 5 describes work within organometallic chemistry and the work was performed at DTU Chemistry under the supervision of Prof. Robert Madsen. Chapter 6 describes work within heteroaromatic chemistry and total synthesis and the work was performed at California Institute of Technology under the supervision of Prof. Brian Stoltz.

- **Chapter 2** describes the retro-Grignard addition reaction with benzylic reagents. This project was performed with very fruitful and enlightening discussions in the company of the very experienced emeritus at DTU Chemistry, Dr. Phil. Torkil Holm. The work was also published in the scientific journal Tetrahedron and the article is attached at the last pages of the thesis.[23]

- **Chapter 3** describes the cleavage of cyclic ethers by Grignard reagents and the project was initiated from observations in the retro-Grignard addition project. The work in this chapter has been accepted for publication in Tetrahedron.[24] The work in chapter 2 and 3 were also presented as a poster in two sessions at the 245th ACS national meeting & exposition, New Orleans, 2013.[25]
- **Chapter 4** combines the fields of bioorganic chemistry and organometallic chemistry and explains further elaboration of the iridium catalyzed dehydrogenative decarbonylation reaction from conditions developed by Ph.D. Esben Olsen and employing this reaction to carbohydrates as a synthetic tool in organic chemistry.
- **Chapter 5** is the most work-intensive chapter in this thesis and the project is concerned with coupling of the dehydrogenative decarbonylation reaction with a palladium catalyzed reductive carbonylation in a two-chamber setup. This project was done in collaboration with Ph.D. Esben Olsen, Bach. Polyt. Samuel Gilbert Elliot and *Cand.* Polyt. Jascha Rosenbuam.
- **Chapter 6** describes work towards the synthesis of tetrahydroisoquinoline alkaloid, (-)-jorumycin, which is a highly potent anticancer agent and also posses antibacterial activity. The work was followed by a group of people in the Stoltz group and my contribution was done in collaboration with Dr. Guillaume Lapointe.

# Chapter 2: The retro-Grignard addition reaction revisited

## 2.1 Background

The addition of Grignard reagents to aldehydes and ketones was discovered by Victor Grignard in 1900.[5] A Grignard reagent is a magnesium halide bound to a carbon compound and has to be prepared prior to the addition step. A similar type of reaction is the Barbier reaction where the nucleophilic reagent is prepared *in situ* and utilizes a broader scope of metals like zinc[26], indium[27] and tin[28]. The Grignard addition reaction is still a commonly employed method for creating a carbon-carbon bond and is performed under strictly anhydrous conditions in ethereal solvents (usually diethyl ether or tetrahydrofuran). Besides aldehydes and ketones, the Grignard reagent also reacts with other carbonyl compounds like formaldehyde, carbon dioxide[29], esters[29], amides[30], anhydrides[29] and acid halides[31] and other electrophiles like nitriles[32], imines[33] and epoxides.[34,35] Furthermore a cross coupling reaction with carbon halides is possible using a Ni or Pd catalyst (Figure 5) in the Kumada coupling.[17–20]

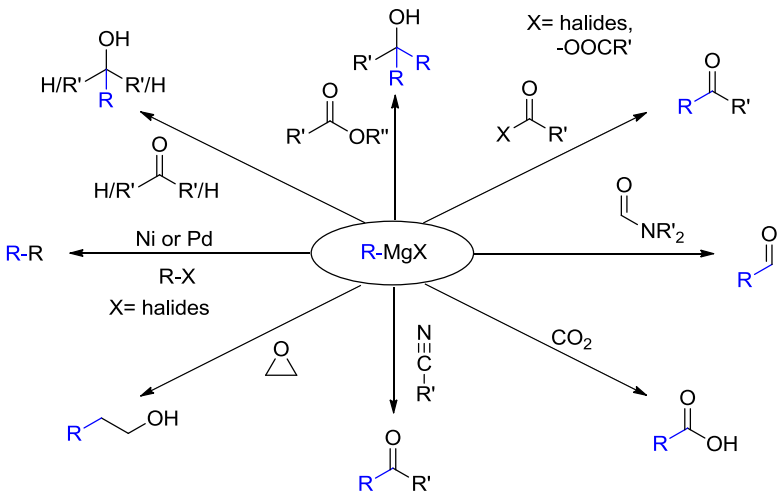
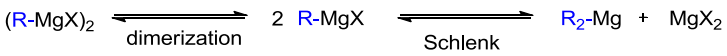



**Figure 5 – Some examples of reactions with a Grignard reagent**

### 2.1.1 Mechanistic information about the Grignard reaction

The exact mechanism of the Grignard addition reaction has been widely discussed over the last century. The amount of literature is overwhelming and only the most relevant for the present work will be presented in this chapter. Organomagnesium halides (or Grignard reagents) are formally represented as R-MgX, where R is the organo part (aliphatic, aromatic etc.) and X is the halide (iodide, bromide, chloride). However, the real identity of the reagent is not so simple. Traditionally, R-MgX exists in two equilibria: the dimerization and the Schlenk equilibrium (Equation 1).[36]




**Equation 1 – Dimerization and Schlenk equilibrium**

The solvent has an important role in these equilibria: the dimerization equilibrium is suggested to be the dominant in $Et_2O$ while the Schlenk equilibrium is suggested to be favored in THF.[37–42] Based on a computational study on the dimer, Yamazaki and Yamabe suggest that one ether ($Me_2O$) molecule is coordinating to each magnesium atom in the thermodynamically most stable species (Figure 6) and they have postulated that this specie is being the reactive species for the Grignard addition.[43] Magnesium in oxidation state II prefer to be tetracoordinated though there seems to be space for further nucleophilic substitutions on the metal atom.

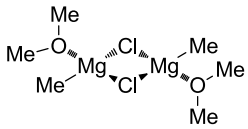



**Figure 6 - Most stable Grignard reagent specie as postulated by Yamazaki and Yamabe**

In the Grignard addition of organomagnesium halides to carbonyl groups, the driving force is the increased stability of the newly formed bonds (O-Mg and C-C) compared to the two broken bonds (C-Mg and C=O). The reagent reacts as a nucleophile and also acts a Lewis acid as the reaction is enhanced when the magnesium halide is coordinating to the carbonyl oxygen. This action makes the carbonyl carbon more electrophilic.

A interpretation of the polar mechanism have been proposed by Ashby and coworkers[44] for the Grignard addition reaction in a review in 1967 (Figure 7) - a modification of the preliminary suggestion by Swain and Boyles[45] that have been proposed in 1951.

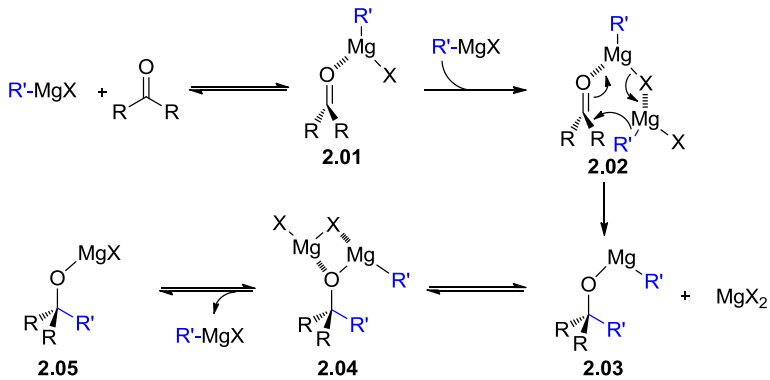



**Figure 7 – Proposed mechanism of the Grignard addition reaction by Ashby (no solvent molecules shown)**

The first Grignard reagent coordinates to the carbonyl oxygen and acts as a complexation agent in **2.01**. After coordination of this agent, a second Grignard reagent coordinates forming complex **2.02**. Cyclic rearrangement forms **2.03**, which rapidly redistributes and the first Grignard reagent dissociates leaving behind the addition product **2.05**. However, the mechanism is more complex than that. A later suggestion, based on the calculation by Yamazaki and Yamabe, have been on the Schlenck dimer and includes two formaldehyde molecules together with two solvent molecules.[43] Interpretation of the mechanism based on calculations without solvent molecules suggests that the cascade is initiated via the bridged dimer **2.06** and the four centered reaction, by a concerted C-C and O-Mg bond formation, occur across the bridge (Figure 8). When intermediate **2.08** is formed, another concerted C-C and O-Mg bond formation produce complex **2.09**. Furthermore, calculations with solvent molecules suggest the similar mechanism to occur now with one $Me_2O$ molecule attached to each magnesium metal. The $Me_2O$ molecules do not affect the polar reaction path significantly, however the calculated bond distance differ between the

two precursors. The covalent and coordination bonds formed to the pentavalent magnesium atoms were comparably loose as opposed to the tight bonds towards the tetravalent magnesium atom.

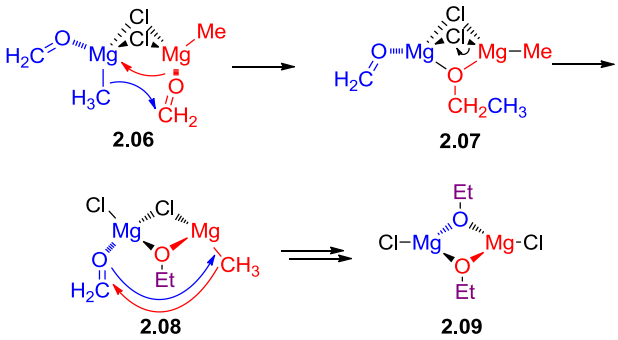



**Figure 8 - Proposed mechanism of the Grignard addition reaction by Yamazaki and Yamabe (no solvent molecules shown)**

Some Grignard reagents, like *t*-butylmagnesium chloride, are known to add by a single-electron transfer (SET) mechanism. This is feasible since the alkyl groups stabilize carbon radicals. A simple proposed mechanism is shown in Figure 9 for the reaction between *t*-butylmagnesium chloride and benzophenone and initiates with the coordination of the Grignard reagent to the carbonyl oxygen.[46] The ketyl radical is formed together with the *t*-butyl radical and recombination of these two radicals forms the 1,2-addition product. The benzopinacol product is also formed and this formation cannot be explained by the polar mechanism. *p*-Dinitrobenzene, which is more easily reduced than benzophenone, will capture an electron from a radical anion whose conjugate ketone has a higher reduction potential. Addition of *p*-dinitrobenzene to the reaction between *t*-butylmagnesium chloride and benzophenone did not affect the rate of the 1,2-addition and the pinacol formation was completely inhibited.[47]

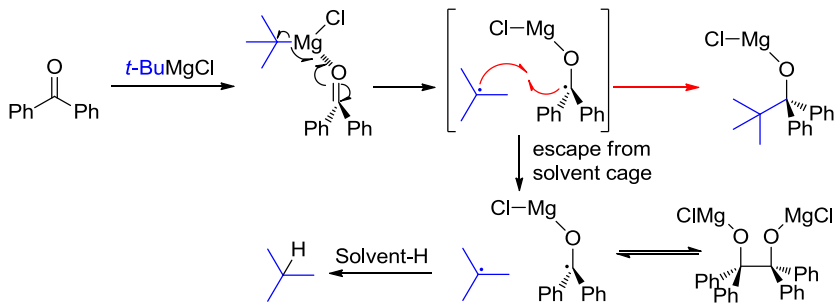
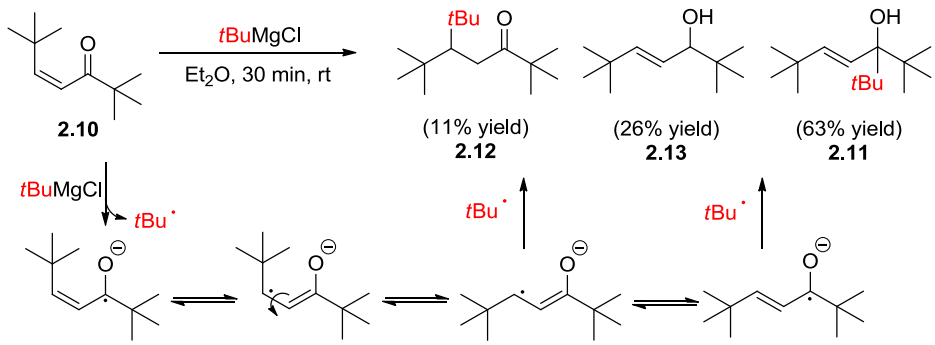



**Figure 9 - Mechanism of the Grignard addition reaction by single-electron transfer**

Another evidence for the SET mechanism have been obtained by adding probes that could detect both radicals. The ketyl radical have been detected with reactions between *t*-butylmagnesium chloride and the *cis*-enone **2.10** because the radical anion isomerized the double bond into a trans configuration in the 1,2-addition product **2.11**, the 1,4-addition product **2.12** and the 1,2-reduction product **2.13** (Scheme 1).[48]




**Scheme 1 - Detection of ketyl radical using a cis-enone probe**

Yamazaki and Yamabe have also calculated the radical pathways in a setup with *t*-butylmagnesium chloride and *cis*-acrolein as the ketone and without solvents although benzophenone would have been better as the ketone.[43] Homolytic cleavage of the C(*t*Bu)-Mg bond from the complex **2.14** occurs while the carbonyl oxygen, bound to the same magnesium atom, and the allyl-radical moiety is being formed (Figure 10). The singlet biradical **2.15** is prepared where the spin densities are located on the tertiary carbon of the t-butyl radical and on the three carbon atoms of acrolein. The two singlet radicals in complex **2.15** have a similar geometries and

similar spin density distributions (with opposite signs) and a radical radical recombination of these two would produce the 1,2-addition and 1,4-addition products.

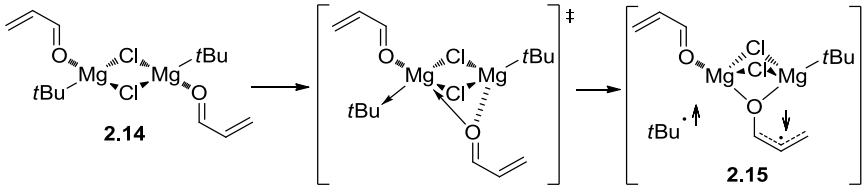


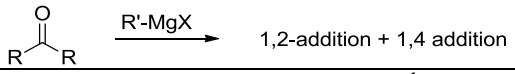

**Figure 10 – Proposed mechanism of the SET by Yamazaki and Yamabe (no solvent molecules shown)**

### 2.1.2 Kinetics

The Grignard addition reaction to ketones is often a very fast reaction. The pseudo first-order rate constants have been determined for various alkylmagnesium halides in the reaction with acetone and benzophenone (Table 1).[37] Low concentration of the ketone substrates are used for these measurements.

Not surprisingly the allyl reagent is the most reactive towards acetone followed by the benzyl, phenyl and then the alkyl reagents (Table 1, entry 1-6). Adding a methyl group in the *para* position of the benzyl group decreases the reactivity (Table 1, entry 4). Usually, acetone reacts faster than benzophenone, although the trend is opposite for *t*-butylmagnesium bromide (Table 1, entry 11). This is a consequence of the different mechanistic pathways. Organomagnesium chloride species are also faster than their corresponding organomagnesium bromide counterparts (Table 1, entry 2-3). Adding magnesium bromide to shift the equilibria towards the dimerization equilibrium (Equation 1, page 10) lowers the reaction rate (Table 1, entry 7-8). The shift in equilibria is supported by the observation that an experiment with dimethyl magnesium and methylmagnesium bromide together with an experiment with dimethyl magnesium both has a higher reaction rate (Table 1, entry 9-10).

**Table 1 - Pseudo first-order rate constant for the conversion of 0.05 M ketone with 0.5 M alkylmagnesium bromide in diethyl ether at 20 °C**




| Entry | R'-MgX | $k'_1$ (acetone) $s^{-1}$ | $k'_1$ (benzophenone) $s^{-1}$ |
|---|---|---|---|
| 1 | AllMgBr | Instant | Instant |
| 2 | BnMgBr | 150 | 91 |
| 3 | BnMgCl | - | 350 |
| 4 | *p*MeBnMgBr | 69 | 1.0 |
| 5 | PhMgBr | 42 | 0.3 |
| 6 | EtMgBr | 7.5 | 7.2 |
| 7 | MeMgBr | 3.8 | 0.30 |
| 8 | MeMgBr + $MgBr_2$[a] | - | 0.16 |
| 9 | MeMgBr + $Me_2Mg$[b] | - | 1.40 |
| 10 | $Me_2Mg$[c] | - | 1.60 |
| 11 | *t*-BuMgBr | 0.1 | 27 |

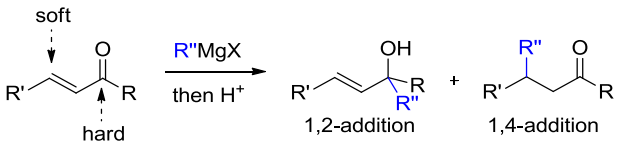
a) 0.57 M MeMgBr and 0.60 M $MgBr_2$. b) 0.57 M MeMgBr and 0.20 M $Me_2Mg$. c) 0.20 M $Me_2Mg$

Grignard reagents are strong bases. Recently in our group, competition experiments have been performed by adding a Grignard reagent to a mixture of a carbonyl compound and protic compound.[49] The rate for the addition of allylmagnesium bromide to acetone is faster than the rate for the protonation with $H_2O$ and the reaction give rise to the addition product in 91% yield. Applying other protic compounds such as methanol, ethanol, phenol and benzoic acid all result in a lower yield of the addition product. Competition experiments with allylmagnesium bromide on a mixture of $H_2O$ as the protic compound and benzaldehyde or methyl benzoate as the carbonyl compound results in a lower yield of the addition product. Furthermore, the competition experiment of benzylmagnesium chloride on a mixture of benzaldehyde and $H_2O$ results in a yield of 89% of the addition product, although the same reagent added to a mixture of acetone and $H_2O$ results in a yield of 30%. *n*-Butylmagnesium bromide is almost completely protonated when added to a mixture of acetone and $H_2O$ or benzaldehyde and methanol. The acidity of magnesium in the Grignard reagent species makes the addition reaction possible in

the presence of $H_2O$ because $H_2O$ is being coordinated to the metal and the protonation reaction becomes less effective.

### 2.1.3 Grignard addition to α,β-unsaturated carbonyl compounds

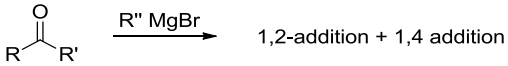
It is well known that nucleophilic addition to an α,β-unsaturated carbonyl compound potentially can result in 2 different products: the 1,2-addition or the 1,4-addition product (Scheme 2). An easy way to predict the product distribution is by establishing whether the nucleophile is a hard or a soft nucleophile although the sterical bulk of the substrates can also affect the outcome. Since the reactions are dominated by electrostatic effects, the Grignard reagents are categorized as hard nucleophiles, and often yield the 1,2-addition product as the carbonyl group is categorized as a hard electrophile. The addition of copper(II) bromide changes the preference into 1,4-addition.[50]

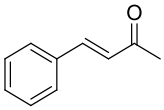
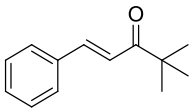
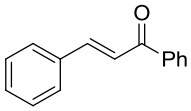



**Scheme 2 - Grignard addition to α,β-unsaturated carbonyl**

Holm have reported the reaction rate and product distribution for the addition of Grignard reagents to several α,β-unsaturated carbonyl compounds together with acetone and benzophenone at room temperature and the most relevant are depicted in Table 2.[51]

**Table 2 - Pseudo first-order rate constant for Grignard addition to α,β-unsaturated ketones**




| Entry | Substrate | MeMgBr | | *n*-BuMgBr | | *t*-BuMgBr | |
|---|---|---|---|---|---|---|---|
| | | $k_1$ ($s^{-1}$) | 1,4-ratio[a] | $k_1$ ($s^{-1}$) | 1,4-ratio[a] | $k_1$ ($s^{-1}$) | 1,4-ratio[a] |
| 1 | acetone | 3.8 | - | 2.2 | - | 0.01 | - |
| 2 | benzophenone | 0.3 | - | 3.2 | - | 27 | - |
| 3 |  | 9 | 16% | 120 | 75% | 46 | 51% |
| 4 |  | 4 | 85% | 1250 | 100% | 22 | 100% |
| 5 |  | 20 | 66% | 11000 | 98% | 14000 | 49% |

a) Ratio of 1,4-addition product in percent: 100%x1,4-addition/(1,4-addition+1,2-addition)

The reaction rates are not significantly increased when comparing acetone with benzophenone using methylmagnesium bromide, but the rates are increased for *t*-butylmagnesium bromide. These observations support the evidence for the SET mechanism as the phenyl groups are better at stabilizing a radical compared to the methyl groups (Table 2, entry 1-2).

The 1,4-addition products can be obtained in two pathways; by a concerted addition mechanism or by a SET mechanism (Figure 11).

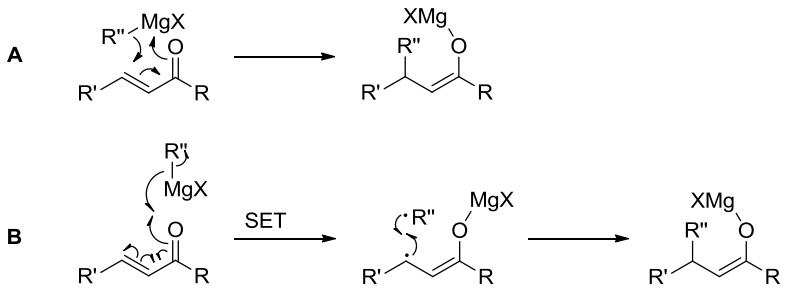



**Figure 11 – Mechanism for 1,4-addition of Grignard reagents to α,β-unsaturated ketones**

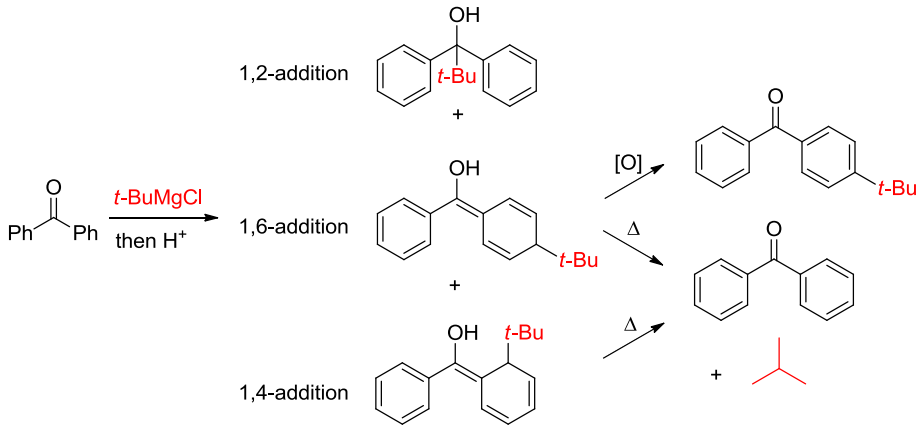
The rate for the addition of *n*-butylmagnesium bromide to benzalacetone is significantly higher (Table 2, entry 3) than for the reaction with acetone or benzophenone. It follows the concerted addition mechanism and it is clear that the cyclic intermediate is important for the increased reaction rates. Methylmagnesium bromide, though, does react in the 1,4-fashion to a lesser extent, due to the "smaller" nucleophile which will attack the hard electrophilic carbon. The reaction rates are not drastically enhanced and the explanation for this is not obvious but can be a consequence of the stronger C-Mg bond in the Grignard reagent. In the addition to benzalpinacolone, the 1,4-addition product is generally highly favored due to the steric bulk present next to the carbonyl group (Table 2, entry 4).

It is clear that the addition of *t*-butylmagnesium bromide mainly follows a radical pathway as the reaction rate is drastically increased when comparing the addition to benzalacetophenone (chalcone) with the addition to benzalpinacolone (Table 2, entry 4-5). This can be explained by the further radical stabilization from the additional phenyl group. The product distribution is for the same reason equally distributed between the 1,2- and the 1,4-addition products.

### 2.1.4 Addition to substituted benzophenones

The addition of *t*-butylmagnesium chloride to benzophenone have three possible products; the 1,2-, the 1,4- and the 1,6-addition product (Scheme 3). Crossland and Holm detected these products by NMR analysis when a complex pattern of absorptions appeared in the vinyl area after anaerobic work-up.[52,53] The 1,4- and the 1,6-addition product were not previously reported since the products are thermo

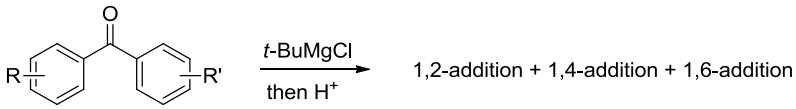
labile as they decompose into benzophenone and isobutene even at room temperature and rapidly at 80 °C. Furthermore, the products have been oxidized in the presence of air into the corresponding alkyl benzophenone, which is a process favored by aromatization.




**Scheme 3 – Addition of *t*-butylmagnesium chloride to benzophenone**

Furthermore, the treatment of benzophenone with *t*-butylmagnesium chloride also yields some benzopinacol product which can be explained by an initial single electron transfer followed by dimerization of two ketyl radicals.[54]

**Table 3 - Product distribution from the reaction of a substituted benzophenone and *t*-butylmagnesium chloride**




| Entry | Benzophenone | benzopinacol | 1,2-addition | 1,4-addition | 1,6-addition |
|---|---|---|---|---|---|
| 1 | Unsubstituted | 6% | 44% | 0% | 50% |
| 2 | 4,4'-Dimethyl | 12% | 55% | 0% | 33% |
| 3 | 4,4'-Di-*t*-butyl | 21% | 40% | 39% | 0% |
| 4 | 2,4,6-Trimethyl | 0% | 0% | 0% | 100% |
| 5 | 2,3,5,6-Tetramethyl | 0% | 0% | 0% | 100% |
| 6 | 2,3,5,4'-Tetramethyl | 0% | 0% | 0% | 100% |

When using substituted benzophenones in the reaction with *t*-butylmagnesium bromide, the steric influence on the product distribution is significant (Table 3). Unsubstituted benzophenone favors 1,2- and 1,6-addition. Adding substituents in both *para* positions of the benzophenone reduces the amount of conjugate addition product compared to the unsubstituted benzophenone. With methyl groups positioned at the *para* positions the 1,6-addition product is still observed, but with the more bulky *t*-butyl groups, the 1,4-addition product is observed instead. It is apparent that substituents on the two *ortho* positions hinders the formation of benzopinacol, as well as the 1,2- and the 1,4-addition products. The sole products observed in these reactions are the 1,6-addition products when using unsymmetrical benzophenones.

Two conformations of benzophenones are proposed; a conrotatory conformation with $C_2$ symmetry and an asymmetric *gauche* conformation where G and G' are in a rapid equilibrium (Figure 12). In unsubstituted benzophenone the dihedral angle between the two benzene rings is 56°.[55] The conjugate addition of a Grignard reagent to a benzophenone must occur in the benzene ring that is conjugated to the carbonyl. Adding bulk to the benzophenone blocks most entrances except the *para* position.

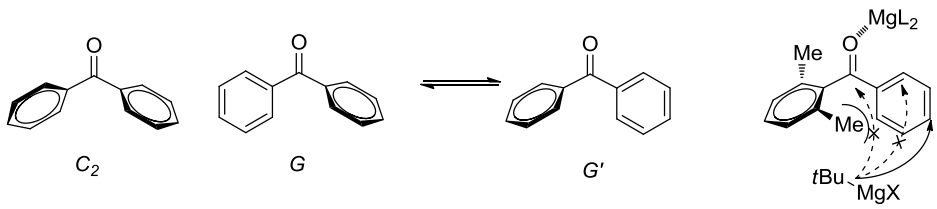
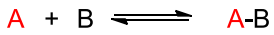



**Figure 12 - conformations of benzophenone**

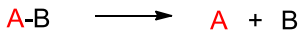
### 2.1.5 The general concept of reversibility

In principle, every process that exists can return to its initial state. In reality this is not always the case. The factors determining this are the thermodynamics and the kinetics. There are several setups to determine whether a chemical reaction is reversible or not (Equation 2).



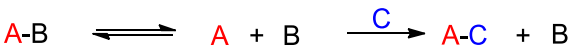

**Equation 2**

The most obvious way would be to recover the starting materials A and B obtained from the adduct A-B of the reaction (Equation 3), but this is often not an option as the adducts usually are more stable than the starting materials.



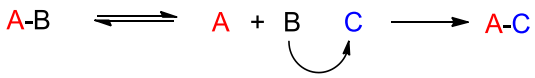

**Equation 3**

Another method is by a scavenging approach where a foreign compound C reacts with one of the fragmented compounds A or B from the reverse reaction (Equation 4). Even if both fragmented compounds are scavenged by different scavengers, this method is not a direct proof of reversibility as the reaction can follow a different pathway (like substitution instead of elimination-addition).




**Equation 4**

In the following example, adduct A-B is initially split into compound A and B. This is followed by compound B converting into a different compound C. If C is also able to combine with A then a new adduct A-C can be formed (Equation 5).

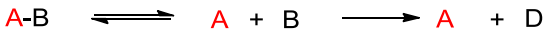



**Equation 5**

If two adducts, with overall four different groups, could be transformed into four compounds scrambling could have occurred. Initially both compounds A-B and A'-B' must be fragmented into four fragments by the reverse reaction. The following recombination would provide two new adducts besides the two starting adducts (Equation 6).


**Equation 6**

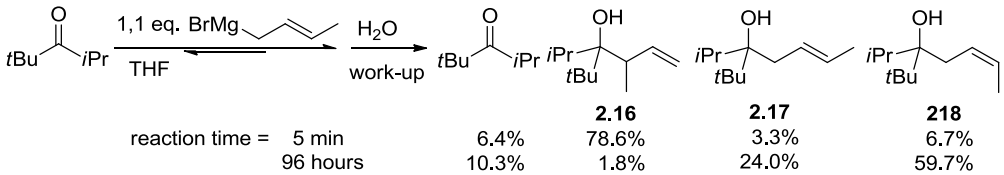
A final example can be if one of the fragments A or B is unstable under certain conditions and the other fragment can be isolated. This test is still not a direct proof as instability of the starting compound can also be the reason for the decomposition (Equation 7).




**Equation 7**

### 2.1.6 Reversibility of the Grignard addition reaction

The Grignard addition reaction have, for a long time, been considered irreversible unless very reactive reagents and sterical hindered substrates have been used. The first example of a reversible Grignard reaction have been discovered by Benkeser and Broxterman in 1969.[56] The reaction of crotylmagnesium bromide with *t*-butylisopropyl ketone shows a different product distribution at different reaction times (Scheme 4).




**Scheme 4 - The reaction of crotylmagnesium bromide with *t*-butylisopropyl ketone**

A short substrate scope analysis have been performed by Benkeser in 1978 and the results indicate that increasing the sterical bulk both on the ketone and the crotyl part also increases the reaction rate of the reverse reaction.[57]

The reaction initially produces the α-methylallyl carbinol **2.16** as the kinetic product, while the thermodynamic products are the less sterically hindered *trans*- and *cis*-crotyl carbinols, **2.17** and **2.18**. The reason for the high reactivity of allylic Grignard reagents is that they form a six-membered cyclic transition state in a $S_N2'$ mechanism.[58] Another factor favoring the $S_N2'$ mechanism over the regular $S_N2$

mechanism is the less steric bulk at the γ-carbon as compared to the α-carbon. The retro-Grignard addition is proposed to form the same transitions state and hence be similar to the Claisen allyl ether rearrangement. A possible explanation for the formation of **2.17** and **2.18** is through a reverse 1,6-cycloaddition followed by a readdition via a four-member cyclic transition state (Figure 13, **A**). It is rather believed that it is due to the crotylmagnesium halide being liberated from the ketone and then is in equilibrium with the methylallylmagnesium halide which performs the readdition (Figure 13, **B**). The latter pathway follows the principle in Equation 5.

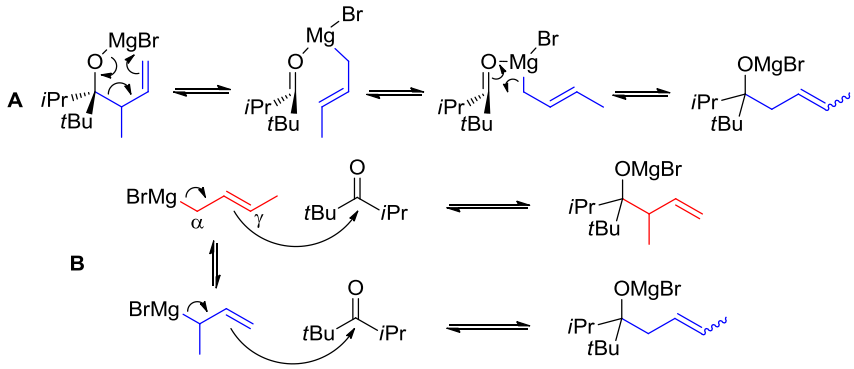
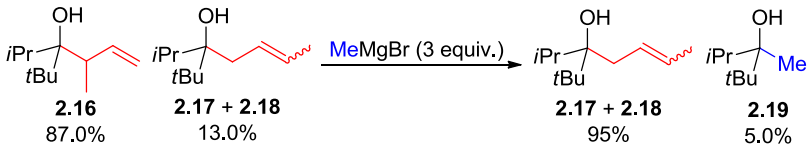


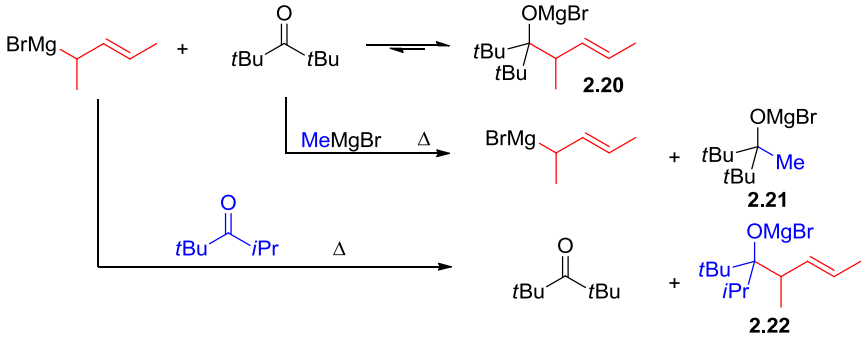

**Figure 13 - Mechanistic consideration in the reaction of crotylmagnesium bromide with *t*-butyl isopropyl ketone**

These experiments, however, are not sufficient to determine whether the rearrangement was due to the retro-Grignard addition or a consequence of a different pathway like a 1,3-radical type rearrangement of the allylic system. Benkeser and Broxterman have also discovered that treating an alcohol mixture of **2.16**, **2.17** and **2.18** with three equivalents of methylmagnesium bromide results in 95% combined yield of the *trans*- and *cis*-crotyl carbinols **2.17** and **2.18,** but also less than 5% of **2.19** where methyl is added. Unfortunately, temperature and reaction times have not been reported in this work.




**Scheme 5 - The reaction of an alcohol mixture with 3 equivalent of MeMgBr**

Further investigation have been performed by Holm in 1976 examining the addition of an allylic Grignard reagent to di-*t*-butyl ketone (Scheme 6).[59] A direct evidence for the reversibility of the reaction would require isolation of the starting materials from the decomposition of product. This, however, is unachievable as the equilibrium is greatly shifted towards the carbinol product. Instead, indirect evidence is obtained by scavenging the starting materials into more stable compounds.

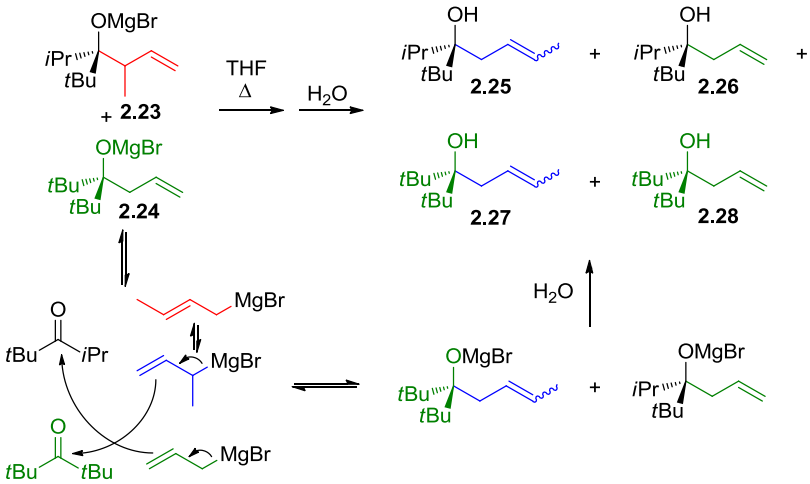



**Scheme 6 - Retro-Grignard addition by foreign Grignard exchange and foreign ketone exchange**

When heating **2.20** with an excess of methyl magnesium bromide, the dimethylallyl group is displaced by the methyl group and **2.21** is formed. When heating **2.20** with the less bulky isopropyl-*t*-butyl ketone, the products obtained are pentenyl-isopropyl-*t*-butyl carbinol (**2.22**) and di-*t*-butyl ketone (Scheme 6). These two reactions are following the principle in Equation 4 as **2.20** needs to split into di-*t*-butyl ketone and 1-methylcrotylmagnesium bromide to be able to react with the foreign additives.

Simultaneously, Benkeser and Siklosi provided further examples of the retro-Grignard addition reaction, where the first example was with an unsubstituted allyl tertiary alcohol.[60] This is performed by a cross-over experiment in which refluxing a mixture

the alkoxide **2.23** together with **2.24** in THF results in a mixture of 6 compounds, **2.25**, **2.26**, **2.27** and **2.28** (cis + trans compounds included) (Scheme 7). This experiment follows the principle in Equation 6.




**Scheme 7 - Crossover experiment**

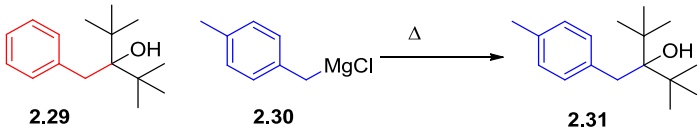
It is certain that the allyl and the butenyl groups have interchanged positions and that the previously observed rearrangement of alkoxide **2.23** into **2.25** also occurs. None of the methylallyl carbinol derived from protonation of **2.23** have been observed. The mechanism is not firmly established but one can postulate that both substrates must be split, followed by additions to form the scrambled products.

It should be noted that several retro-allylation reactions with metals other than magnesium have been reported but this will not be included in this thesis.[61,62]

### 2.1.7 Project idea

As described *vide supra* the retro-Grignard addition has only been observed with bulky ketones and crotyl substrates and hence this project will be to investigate the repertoire of available substrates and reaction conditions available for this reaction. The substrates chosen are preferably bulky as well and the leaving group will still need to be very reactive. In the Grignard addition to acetone, the relative reactivity of the Grignard reagents are as described *vide supra*: allyl > benzyl > phenyl > alkyl.[51]

Since the crotyl group as leaving group has been thoroughly investigated, this project will be based on the retro-Grignard addition of the allyl- and the benzyl group. Preliminary results by Dr. Torkil Holm demonstrated the conversion of di-*t*-butyl-benzyl methanol into di-*t*-butyl-tolyl methanol when heated with *p*-methylbenzylmagnesium bromide at 100 °C (Scheme 8).




**Scheme 8 – retro-Grignard addition with benzylic substrates**

Grignard additions by an electron transfer mechanism may also be reversible although this scenario is more complicated since two consecutive steps are involved. *t*-Butylmagnesium chloride serves as a good Grignard reagent and mesitylphenyl ketone and benzalpinacolone as good radical acceptors. Both ketones are known to react with *t*-butylmagnesium chloride and afford only one product. Benzalpinacolone gives exclusively the 1,4-addition product in this case, while mesitylphenyl ketone only furnishes the corresponding 1,6-adduct. The latter is strained and lacks aromatic stabilization making it a good candidate for a reverse addition reaction.

## 2.2 Results and discussion

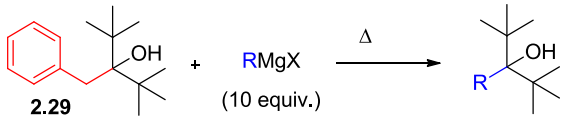
### 2.2.1 Reactions of di-*t*-butyl-benzyl methanol with Grignard reagents

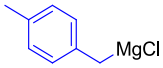
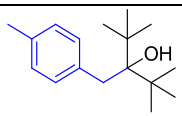
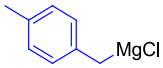
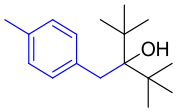
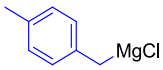
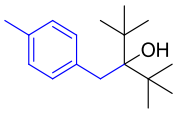
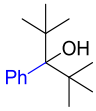
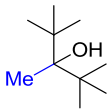
The initial goal in this project was to reproduce the preliminary results from Dr. Torkil Holm. The starting material was easily prepared by adding benzylmagnesium bromide to di-*t*-butyl ketone at room temperature in diethyl ether. Due to the sterical bulk the reaction was allowed to stand overnight. Benzylmagnesium bromide was commercially available but the quality of the reagent can be better if it is freshly prepared. Reference compounds were also formed by the Grignard addition reaction.

The initial attempts to recreate the preliminary results were not successful (Scheme 8). The tertiary alcohol **2.29** and 4-methylbenzylmagnesium bromide (0.5 M in THF) were mixed and heated to 100 °C in a sealed vessel, but no conversion of the alcohol **2.29** was observed. When the reaction temperature was increased to 120 °C low conversion was observed after 2 days of reaction time. Higher temperature was applied with care as the sealed tube might not withstand the elevated pressure. A better result was achieved at 140 °C, and after 3 days the substituted product was obtained in 51% yield (Table 4, entry 1). After a total of 10 days the starting material was fully converted and the yield of the product was 77% (Table 4, entry 2).

Phenylmagnesium bromide in THF was reacted with **2.27** at 140 °C for 10 days, but this resulted in a low yield of 7% of the exchanged product (Table 4, entry 4). The reaction also produced a multitude of byproducts according to the GC chromatogram, and further investigation with this reagent was therefore abandoned. $(t\text{Bu})_2$(Ph)COH was not formed by the addition of phenylmagnesium bromide to di-*t*-butyl ketone using the same conditions as the formation of the other tertiary alcohols. The tertiary phenyl alcohol was instead prepared by using the smaller nucleophile, phenyl lithium, on di-*t*-butyl ketone. The reluctance for $(t\text{Bu})_2$(Ph)COH to be prepared by a Grignard addition might explain the sluggish substitution of **2.29** with the phenyl group.

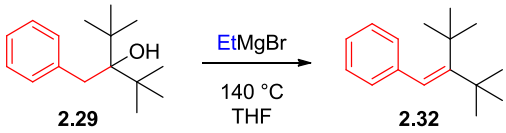
**Table 4 - Reactions of di-*t*-butyl-benzyl methanol with Grignard reagents**




| Entry | RMgX | t (°C)[a] | T | Product | Yield[b] | Yield **2.19**[b] |
|---|---|---|---|---|---|---|
| 1[c] |   | 140 °C | 3 d |   | 51% | 48% |
| 2[c] |   | 140 °C | 10 d |   | 77% | 0% |
| 3[c] |   | 190 °C | 18.5 h |   | 48%[d] | 52%[d] |
| 4[e] | PhMgBr | 140 °C | 10 d |   | 7% | 57% |
| 5[f] | MeMgBr | 140 °C | 6 d |   | 75% | 29% |
| 6[e] | EtMgBr | 140 °C | 6 d | - | 0% | 39% |
| 7[g] | none | 150 °C | 3 d | - | | 100% |

a) Temperature is set in a separate vial with silicone oil by heating the reaction vessels in an aluminum block. b) Yield based on GC chromatogram using standard curves from compounds and using *n*-nonane as internal standard. c) 0.67 M Grignard reagent in THF. d) ratio of the two compounds, no internal standard used. e) 1.0 M Grignard reagent in THF. f) 3.0 M Grignard reagent in $Et_2O$. g) In $Et_2O$.

Though methylmagnesium bromide is a weaker nucleophile than the benzylic reagents it was also applied with success resulting in 75% yield after 6 days at 140 °C (Table 4, entry 5). However, exchanging with ethylmagnesium bromide was unsuccessful (Table 4, entry 6) because some of alcohol **2.29** was converted into the eliminated product **2.32** (Scheme 9). This would probably also be the case for other alkylmagnesium halides with a β-proton and consequently similar alkyl reagents were not applied.

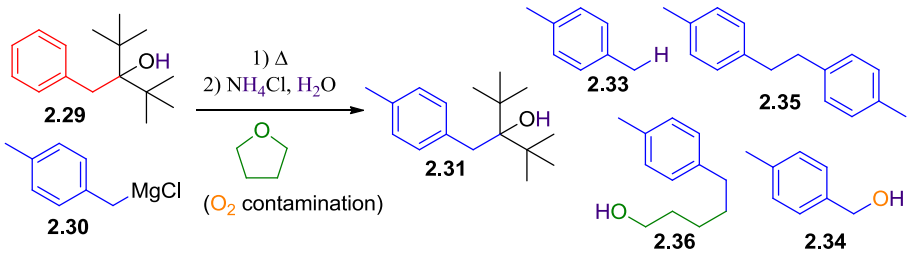



**Scheme 9 - Elimination**

A stability test of the starting material was also performed and no degradation was observed according to the GC chromatogram when heating at 150 °C for 3 days (Table 4, entry 7).

Observed organic byproducts from this conversion are (Scheme 10):

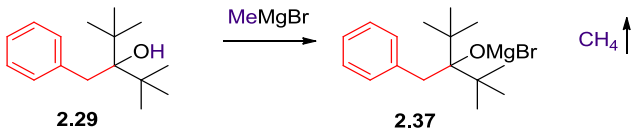
- Xylene (**2.33**) which originates from the quenched Grignard reagent with either **2.29** or during the acidic work-up.
- 4-Methylbenzyl alcohol (**2.34**) which is produced by oxidation of the Grignard reagent from $O_2$ contamination.
- Bi-*p*-xylene (**2.35**) as the Wurtz product from the generation of the Grignard reagent.
- Unexpected product **2.36** where the tetrahydrofuran ring opens combined with addition of xylene. Heating the Grignard solution alone at 140 °C produced this in high yield, and gives rise to a new project which will be described in chapter 3.




**Scheme 10 - Products formed**

### 2.2.2 Reactions of magnesium di-*t*-butyl-benzylmethanolate bromide with ketones

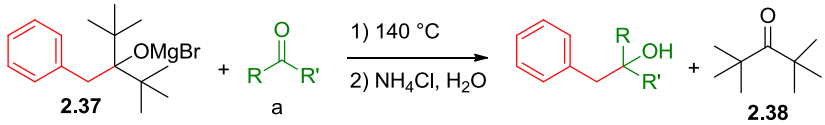
The satisfying result in the previous section was not sufficient to declare the reaction to be reversible. Experiments have been performed in an attempt to expel the benzyl group and insert this to a less sterical hindered ketone. Initially, the starting compound was generated by adding methylmagnesium bromide to di-*t*-butyl-benzyl carbinol **2.29** (Scheme 11).

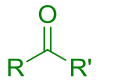
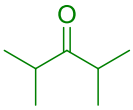
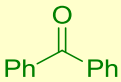
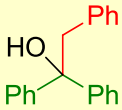
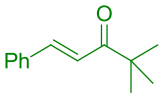
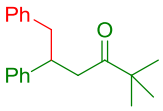
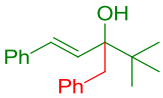



**Scheme 11 - Generation of alkoxide**

Methane gas was developed instantaneously and was briefly allowed to evaporate. After generation of the starting material the ketone was added and the reaction was heated. A summary of the reactions is shown in Table 5. Acetone is one of the least sterically hindered ketones but under the basic conditions in the reaction mixture, acetone would undergo self condensation and therefore more stable ketones were required. Diisopropyl ketone is more stable towards self condensation but still no conversion was observed in this reaction (Table 5, entry 1). Though no self condensation products are formed in the reaction, the enolate may still be formed in the mixture making it inert towards nucleophilic attack. Benzophenone could potentially extract the benzyl group from **2.37** as enolate formation is not occurring in this substrate. The exchange product was indeed formed in 40% yield while di-*t*-butyl ketone (**2.38**) was produced in 60% yield (Table 5, entry 2). This result clearly indicated that the benzyl group still had the ability to make a nucleophilic attack after separation from **2.37**.

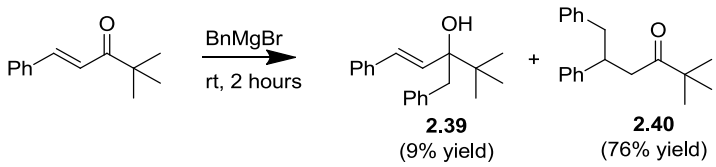
**Table 5 - Reactions of magnesium di-*t*-butyl-benzylmethanolate bromide with ketones**




| Entry |  | T (d) | Products | Yield[c] |
|---|---|---|---|---|
| 1 |  | 3 | No reaction | - |
| 2 |  | 3 |  **2.38** | 40% 60% |
| 3 |  | 3 |   **2.38** | 11% 5% 27% |
| 4 | none | 8 | **2.38** | 62% |

a) Excess ketone used. b) Temperature is set in a separate vial with silicone oil by heating reaction vessels in an aluminum block. c) Yield based on GC chromatogram using standard curves from compounds and using n-nonane as internal standard.

Benzalpinacolone was also able to accept the benzyl group from **2.37** after 3 days at 140 °C in a total yield of 16% (Table 5, entry 3). The selectivity was slightly favored towards the 1,4-addition product **2.40** compared to the 1,2-product **2.39**, but the reaction was much less selective than the addition of benzylmagnesium bromide to benzalpinacolone (Scheme 12). This was probably a consequence of the different temperatures and not the nature of the nucleophile.

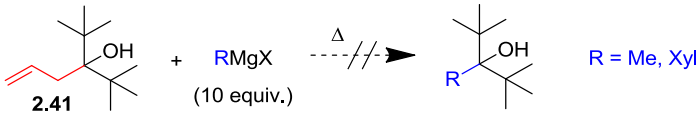



**Scheme 12 - Addition of benzylmagnesium bromide to benzalpinacolone**

A quite puzzling result was obtained when heating the starting material without a foreign ketone as it decomposed into the ketone and toluene (Table 5, entry 4). In theory the benzyl group should be able to return to reform the starting material, but the inability is probably due to decomposition of the benzyl part of the split product.

### 2.2.3 Reactions of di-*t*-butyl-allyl methanol with Grignard reagents

To further expand the repertoire of Grignard reagents able to substitute the allyl group other than the previously described allylic reagents, some of the same reagents as employed in section 2.2.1 were used (Scheme 13). No conversion of **2.41** was observed in reactions up to 70 °C and higher temperatures were not attempted since the allyl group is not thermostable. The allyl reagent is much more reactive than all other types of reagents, and if the retro-Grignard addition occurs, the allyl group would instantaneously add again.

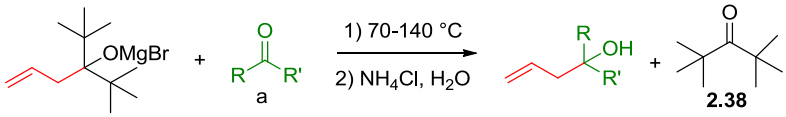


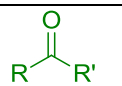
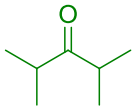
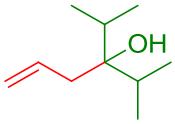
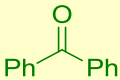
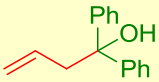
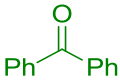
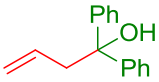
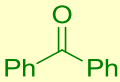
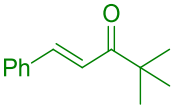
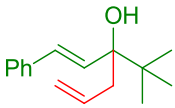
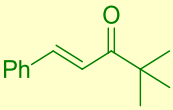
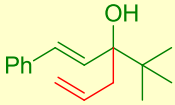

**Scheme 13 - No exchange of the allyl group**

### 2.2.4 Reactions of magnesium di-*t*-butyl-allylmethanolate bromide with ketones

Despite the inability of a foreign reagent to substitute the allyl group, it was possible to transfer the group into other ketones. The starting material was produced with the reaction of 1 equivalent of methylmagnesium bromide with di-*t*-butyl-allyl methanol as shown previously (Scheme 11, Page 30).

**Table 6 - Reactions of magnesium di-*t*-butyl-benzylmethanolate bromide with ketones**




| Entry |  | t (°C)[b] | T | Products | Yield[c] |
|---|---|---|---|---|---|
| 1 |  | 70 | 18 h |  | 34% |
| | | | | **2.38** | 29% |
| 2 |  | 140 | 10 min |  | 85% |
| | | | | **2.38** | 70% |
| 3 |  | 70 | 19 h |  | 32% |
| | | | | **2.38** | 28% |
| 4 |  | rt | 5 d | No reaction | - |
| 5 |  | 70 | 19 h |  | 50% |
| | | | | **2.38** | 52% |
| 6 |  | 55 | 24 h |  | 20% |
| | | | | **2.38** | 20% |

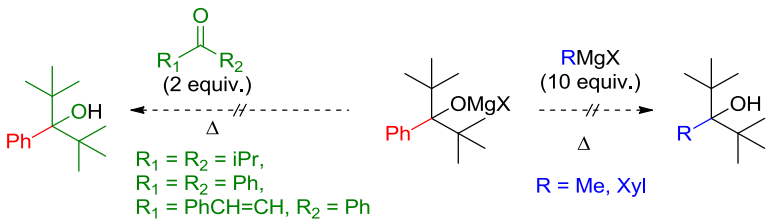
a) Excess ketone used. b) Temperature is set in a separate vial with silicone oil by heating reaction vessels in an aluminum block. c) Yield based on GC chromatogram using standard curves from compounds and using n-nonane as internal standard.

It was possible to scavenge the allyl group into diisopropyl ketone, benzophenone and benzalpinacolone (Table 6). No reaction occurred at room temperature and moderate yields were observed at 70 °C after a reaction time of about 19 hours (Table 6, entry

3-4). Heating the mixture with benzophenone at 140 °C for 10 minutes resulted in a high yield and almost full conversion (Table 6, entry 2). The exchange reactions with benzalpinacolone only yielded the 1,2-addition product as expected.

### 2.2.5 Reactions of di-*t*-butylphenyl methanol and the corresponding magnesiummethanolate bromide

Since di-*t*-butylphenyl methanol was not produced by the Grignard addition but by addition with phenyllithium (see section 2.2.1), probably due to steric hindrance, it could potentially be a substrate for the retro-Grignard addition. Experiments showed no conversion of any of the starting materials at 140 °C, when using ketones or Grignard reagents (Scheme 14). The possibility of making a retro-Grignard addition with the phenyl group as the leaving group cannot be excluded as it might happen at a higher temperature. Due to safety reasons and with an increased amount of byproducts generated at higher temperatures, no further experiments were performed.




**Scheme 14 - Reactions of di-*t*-butylphenyl methanol and the corresponding methanolate bromide**

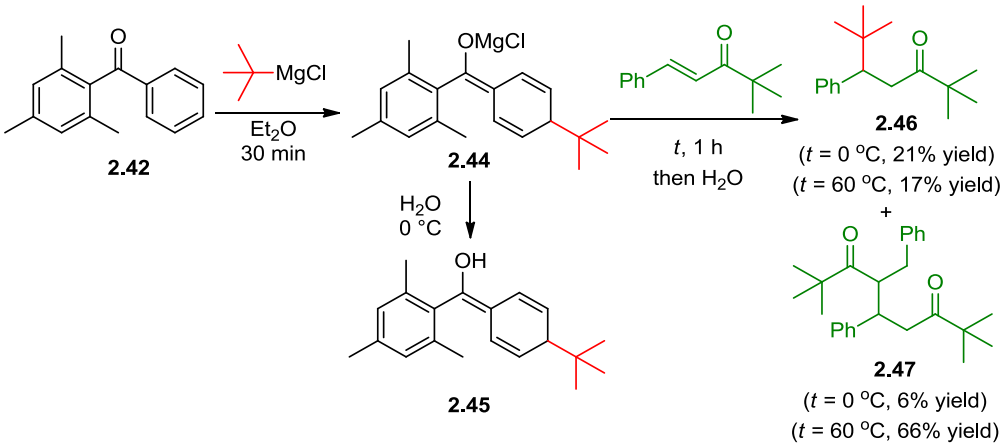
### 2.2.6 Reactions of benzophenone additives of *t*-butylmagnesium chloride

This series of experiments were performed to test whether or not the retro-Grignard addition can be detected from the SET mechanism, and therefore reagents prone to follow this pathway were selected. *t*-Butylmagnesium halides are known to make the addition following this pathway and were chosen as the leaving group. Adding this radical to a sterical hindered benzophenone would generate a rather unstable 1,6-addition compound which wsould be used as substrate in the retro-Grignard addition.[52] Benzalpinacolone was used as the scavenger of the radical as the addition

of *t*-butylmagnesium chloride to benzalpinacolone was reasonably fast and produced only the 1,4 addition product.[51]

Mesitylphenyl ketone (2,4,6-trimethyl benzophenone, **2.42**) and dimesityl ketone (2,2',4,4',6,6'-hexamethyl benzophenone, **2.43**) were prepared by a Friedel-Craft acylation and distilled in order to avoid any undesired sidereactions from metal impurities.[63,64] When reacting methylmagnesium bromides with benzophenones, even trace impurities of $FeCl_3$ (obtained as an impurity in $AlCl_3$) is sufficient to catalyze the formation of benzopinacol products, especially in the case of the unreactive dimesityl ketone.[65]

In the initial experiments mesitylphenyl ketone (**2.42**) was applied. After generation of the enolate **2.44** with addition of *t*-butylmagnesium chloride to a small excess of the benzophenone, benzalpinacolone were added. It was possible to obtain the enol **2.45** by cold work-up of enolate **2.44** before the addition of benzalpinacolone under an inert atmosphere. NMR-experiments clearly showed that the benzophenone was fully converted after 30 minutes.




**Scheme 15 – First benzophenone exchange studies**

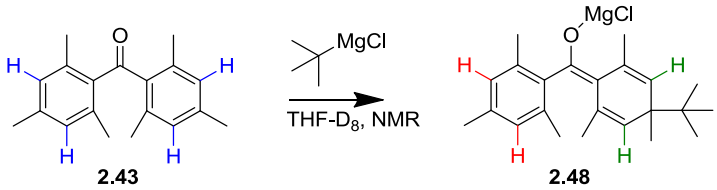
At 0 °C the main product formed was the 1,4-addition product **2.46,** but at 60 °C a substantial amount of dimer **2.47** was formed. To confirm that the formation of **2.46** and **2.47** was not a result of unreacted *t*-butylmagnesium chloride, an additional

experiment using an excess of mesitylphenyl ketone (**2.42**) was carried out which still formed the two products. However, a lower reaction rate was observed in this case. The reaction was followed by taking aliquots out at certain times and analyzing the samples by GCMS. The analysis showed that the reaction progressed over time.

Not surprisingly, the reactions could also be performed by using amylmagnesium chloride instead of *t*-butylmagnesium chloride. This was performed as a proof of concept to establish that the *t*-butyl radical was not the only reagent applicable, although this was not further elaborated.

Dimesityl ketone (**2.43)** is more sterically hindered and as a result the addition of *t*-butylmagnesium chloride to this ketone produced the 1,6-addition product **2.48** at a lower rate than the addition to mesitylphenyl ketone **2.42**. The addition rate was followed by $^{1}$H-NMR-spectroscopy by using a small excess of dimesityl ketone **2.43** compared to *t*-butylmagnesium chloride (Scheme 16). Figure 14 showed the aromatic and double-bond part of the $^{1}$H-NMR-spectra after 1 scan (6.5 minutes), 75 scans (approximately 8 hours) and 149 scans (approximately 16 hours) and the full spectrum is added in the appendix.

In this area, the major singlet signal at 7.01 ppm disappeared while new signals appeared at 6.87, 5.13 and 5.00 ppm. The signal at 7.01 ppm originated from the 4 aromatic protons in dimesityl ketone. The signal at 6.87 ppm was from the 2 aromatic protons in the formed compound and the latter two signals were from the 2 enolic protons in the product. Following the course of the reaction by using the definite integrals of the signals from the protons mentioned gave us the following graph (Figure 15).




**Scheme 16 - Addition of *t*-butylmagnesium chloride to dimesityl ketone (2.43)**

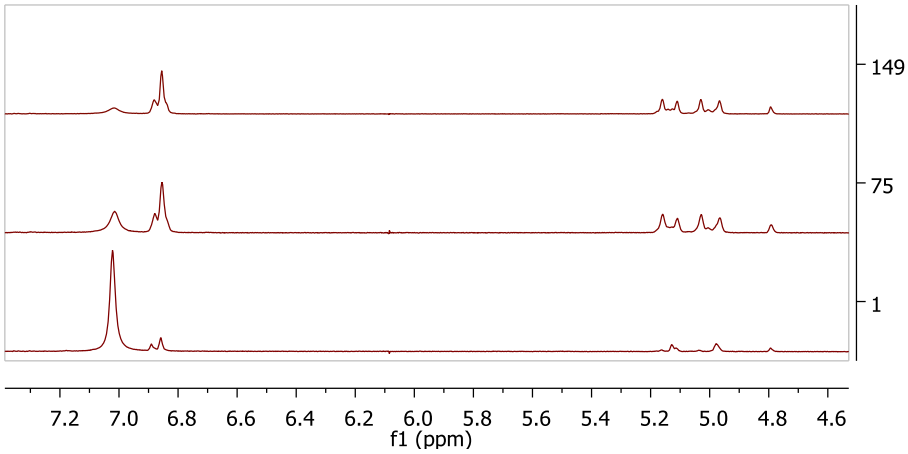



**Figure 14 - Addition of *t*-butylmagnesium chloride to dimesityl ketone. y-Axis show the number of scans, 1 scan equals 6.5 minutes of reaction time. (full spectra shown in appendix)**

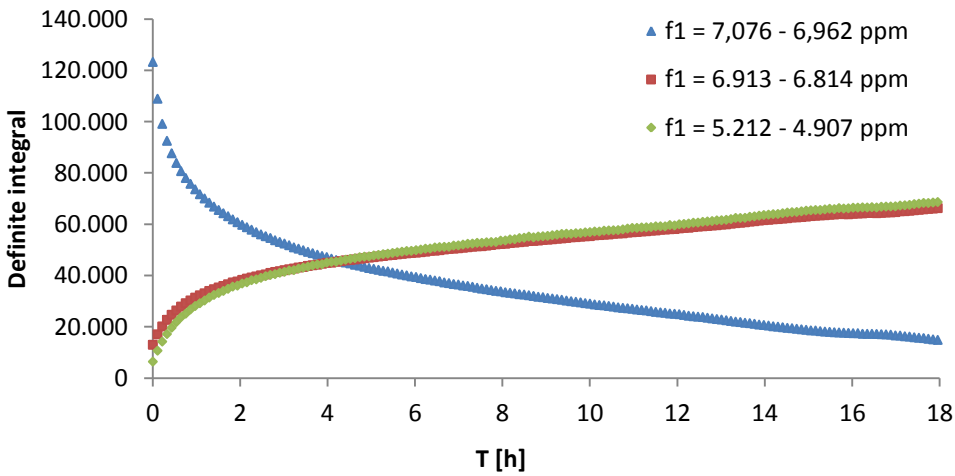
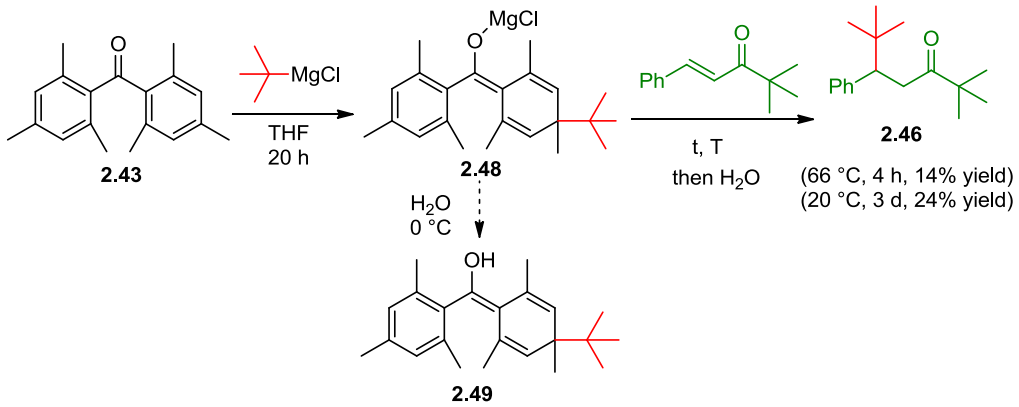



**Figure 15 - Graph of the definite integral of selected protons in the addition of *t*-butylmagnesium chloride to dimesityl ketone**

It appeared that the reaction was approaching completion after 18 hours. Full conversion was not expected as a substoichiometric amount of *t*-butylmagnesium chloride was applied.

As the product formed was highly unstable it was not possible to isolate the enol **2.49** after cold work-up under inert atmosphere (Scheme 17). An attempt to obtain a crystal structure of the enol **2.49** resulted in the structure of dimesityl ketone **2.43**.

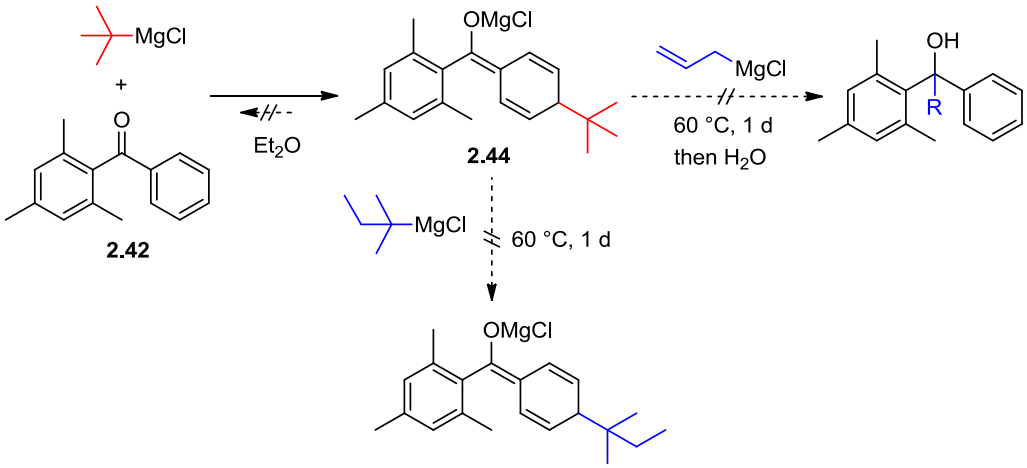



**Scheme 17 – Second benzophenone exchange studies**

It was also possible to extract the *t*-butyl radical from magnesium enolate **2.48** into benzalpinacolone forming the 1,4-addition product **2.46** (Scheme 17). Heating the reaction at reflux for 4 hours gave **2.46** in 14% yield while at room temperature for 3 days the yield was 24%. The reaction was also followed over time and progress in the formation of product **2.46** was observed. In all these cases the dimer **2.47** was not observed.

Again, it was not sufficient to establish that the true pathway was the retro-Grignard addition pathway only by the ketone exchange experiments performed. Reactions for exchanging the Grignard reagent were set-up. Allylmagnesium chloride would rapidly add to any existing mesitylphenyl ketone in the solution. Furthermore, the 1,2-addition product formed would presumably be more stable due to aromatization. However, no transformation was observed when an excess of allylmagnesium

chloride was added to **2.44**, even at 60 °C (Scheme 18). One could also imagine the possibility of exchanging the *t*-butyl group with a different tertiary radical, however the use amylmagnesium chloride did not form any new addition product.




**Scheme 18 - Grignard reagent exchange studies**

From the latter results it was obvious that the formation of **2.46** and **2.47** (Scheme 15) is not a result of a true retro-Grignard addition reaction. A different reaction pathway was postulated. As the classical SET mechanism, the initial step in this case was the electron transfer from the magnesium complex to the carbonyl oxygen on benzalpinacolone (Figure 16). Complex **2.50** was made and this intermediate was split into mesitylphenyl ketone (**2.42**) and the *t*-butyl radical. At 0 °C the latter radical and the magnesiumenolate radical **2.51** were combined and formed the 1,4-addition product **2.46**. At 60 °C, **2.51** was able to diffuse out of the solvent cage and add to another molecule of benzalpinacolone forming compound **2.52**. An electron was extracted presumably from **2.44** and the final product was the dimer **2.47** after work-up.

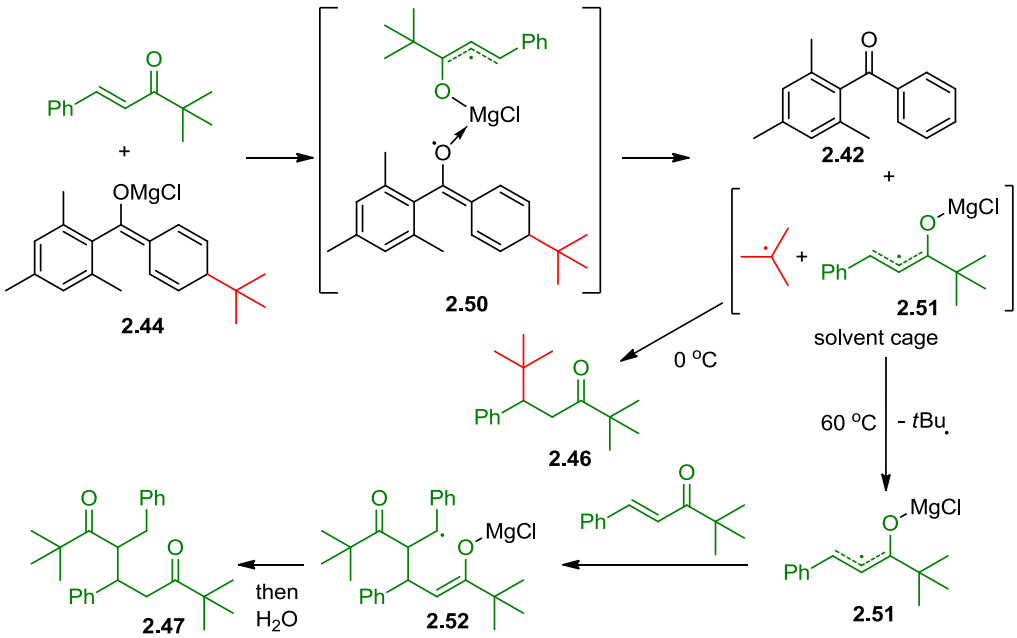



**Figure 16 - Suggested mechanism**

## 2.3 Conclusion

The work described in this chapter further expands the scope of a retro-Grignard addition reaction from the existing examples. The benzyl group was successfully exchanged by the *p*-methylbenzyl, phenyl and methyl groups while the allyl group was not exchanged by any of the latter groups. The benzyl and allyl groups were both able to be extracted into ketones from the hindered alkoxide substrate. These results suggest that the retro-Grignard reaction is possible by a concerted reaction pathway. The *t*-butyl radical was extracted by benzalpinacolone but the radical could not be exchanged by Grignard reagents. A different reaction pathway for this transformation was suggested.

## 2.4 Experimental section

### 2.4.1 General methods

Ketones were purchased from Sigma-Aldrich and used as received. Benzylic Grignard reagents were prepared in ampoules by slow addition of the benzylic halide to a magnesium suspension in freshly distilled THF under an argon atmosphere. The remaining Grignard reagents were purchased from Sigma-Aldrich and used as received. The base concentration was determined by quenching 1.0 mL of the solution in $H_2O$ followed by addition of a few drops of phenolphthalein and then titrating with nitric acid until a color shift from pink to colorless occurred.[66] THF was distilled from sodium and benzophenone while $Et_2O$ was dried over sodium. Magnesium turnings were dried under high vacuum while glassware was dried in an oven at 185 °C. NMR spectra were recorded on a Varian Mercury 300 or a Bruker Ascend 400 spectrometer with residual solvent signals as reference. Melting points were measured on a Stuart SMP30 melting point apparatus and are uncorrected. Mass spectrometry was performed by direct inlet on a Shimadzu QP5000 GCMS instrument fitted with a Equity 5, 30 m × 0.25 mm × 0.25 μm column. High resolution mass spectra were recorded on a Agilent 1100 LC system which was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with a Lock Mass probe. Visualization was done by dipping into a solution of $KMnO_4$ (1%), $K_2CO_3$ (6.7%) and NaOH in $H_2O$, or a solution of $H_2SO_4$ (10%) in $H_2O$, followed by heating with a heatgun. Flash chromatography was performed with silica gel 60 (35-70 μm).

### 2.4.2 General procedure for the synthesis of tertiary alcohols

The ketone was dissolved in $Et_2O$ and a small excess of the Grignard solution in $Et_2O$ or THF was added under an argon atmosphere. The reaction was stirred overnight at room temperature. The mixture was diluted with $Et_2O$ and quenched with $H_2O$. The organic layer was separated and washed with saturated aqueous $NH_4Cl$ and $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated. Further purification was performed either by vacuum distillation or by column chromatography (heptane/EtOAc or heptane/toluene).

### 2.4.3 General procedure for Grignard exchange reactions

3-Benzyl-2,2,4,4-tetramethylpentan-3-ol (**2.29**) (65 mg, 0.28 mmol) was added to a 5 mL screw-top vial which was flushed with argon. The Grignard reagent solution (4.0 mL of 0.67 M *p*-methylbenzylmagnesium chloride in THF, or 4.0 mL of 1.0 M phenylmagnesium bromide in THF, or 2.5 mL of 3.0 M methylmagnesium bromide in $Et_2O$) was then added and the vial sealed. The solution was heated to 140 °C for the indicated time. The mixture was then allowed to reach room temperature and the reaction diluted with $Et_2O$ and quenched with $H_2O$. The organic layer was separated and washed with saturated aqueous $NH_4Cl$ and $H_2O$. Samples for GC analysis were taken out and yields were determined by using calibration curves with *n*-nonane as internal standard.

### 2.4.4 General procedure for ketone exchange reactions

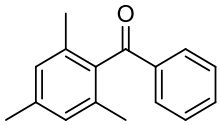
3-Benzyl-2,2,4,4-tetramethylpentan-3-ol (**2.29**) (79 mg, 0.34 mmol) was placed in a 5 mL screw-top vial which was flushed with argon. $Et_2O$ (1.0 mL) and methylmagnesium bromide (0.11 mL, 3.0 mL in $Et_2O$, 0.33 mmol) were added. When the gas evolution had ceased benzophenone (260 mg, 1.43 mmol) was added. The vial was sealed and heated at 140 °C for 10 days. Then the mixture was allowed to reach room temperature and the reaction was diluted with $Et_2O$ and quenched with $H_2O$. The organic layer was separated and washed with saturated aqueous $NH_4Cl$ and $H_2O$. A sample for GC analysis was taken out and yields were determined by using calibration curves with *n*-nonane as internal standard.

### 2.4.5 General procedure for *t*-butyl exchange reactions

To mesitylphenyl ketone (**2.42**) (525 mg, 2.34 mmol) in dry $Et_2O$ (10.0 mL) was added *t*-butylmagnesium chloride (1.5 mL, 1.25 M in $Et_2O$, 1.90 mmol) under an argon atmosphere. The light brown suspension was stirred at room temperature for 30 min. The reaction was set to the indicated temperature and benzalpinacolone (358 mg, 1.90 mmol) was added. The reaction was stirred at this temperature for 1 hour. The mixture was diluted at room temperature with $Et_2O$ and quenched with $H_2O$. The organic layer was separated and washed with saturated aqueous $NH_4Cl$ and $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated. A sample for GC

analysis was taken out and yields were determined by using calibration curves with *n*-nonane as internal standard.

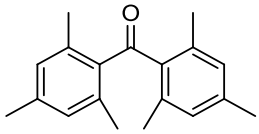
### 2.4.6 Formation of mesitylphenyl ketone (2.42)



$AlCl_3$ (25.0 g, 188 mmol) was suspended in mesitylene (50 mL, 0.360 mol) under a nitrogen atmosphere and the suspension was cooled to 0 °C. Benzoyl chloride (19.5 mL, 168 mmol) was added over 30 minutes and during this time the mixture turned into a red slurry mass. The reaction was heated at 60 °C for 21 hours. The mixture was poured into a concentrated HCl/ice mixture and stirred for 30 minutes. The mixture was extracted with $Et_2O$ and washed three times with saturated aqueous $K_2CO_3$ and once with brine. The organic phase was dried with $MgSO_4$, filtered and concentrated. Distillation afforded mesitylphenyl ketone (**2.42)** (35.1 g, 156 mmol, 93%).

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.85 – 7.78 (m, 2H), 7.63 – 7.54 (m, 1H), 7.49 – 7.40 (m, 2H), 6.90 (s, 2H), 2.34 (s, 3H), 2.09 (s, 6H)
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 200.8, 138.5, 137.3, 136.9, 134.2, 133.60, 129.4, 128.8, 128.4, 21.2, 19.4
**IR:** $\nu_{max}$ (film) 2915, 2854, 1666, 1609, 1596, 1579, 1447, 1312, 1267, 1170, 909, 852, 708, 687

### 2.4.7 Formation of dimesityl ketone (2.43)

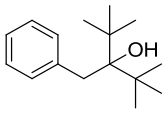


2,4,6-trimethylbenzoic acid (20.0 g, 122 mmol) was dissolved in $SOCl_2$ (20.0 mL, 276 mmol) and heated at reflux for 5 hours under a nitrogen atmosphere. The brown solution was concentrated to form 2,4,6-trimethylbenzoyl chloride which was used immediately in the next step.

$AlCl_3$ (16.79 g, 126 mmol) was suspended in mesitylene (40 mL, 0.288 mol) under nitrogen atmosphere and the suspension was cooled to 0 °C. The freshly prepared 2,4,6-trimethylbenzoyl chloride (19.5 mL, 168 mmol) was added over 30 minutes and the mixture turned into a red slurry mass. The reaction was heated at 60 °C for 18 hours. The mixture was poured into a concentrated HCl/ice mixture and stirred for 30 minutes. The mixture was extracted by $Et_2O$ and washed three times with saturated aqueous $K_2CO_3$ and once with brine. The organic phase was dried with $MgSO_4$, filtered and concentrated. Distillation followed by crystallization (MeOH/toluene) afforded dimesityl ketone (**2.43**) (4.06 g, 15.2 mmol, 12%) as colorless crystals.

**Mp** 137-139 °C, lit. 138-140 °C[67]
**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 6.85 (s, 4H), 2.29 (s, 6H), 2.13 (s, 12H)
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 202.7, 140.1, 138.5, 136.6, 129.9, 21.2, 20.8
**IR:** $\nu_{max}$ (film) 2966, 2918, 1643, 1607, 1569, 1424, 1377, 1281, 1263, 1242, 1163, 1029, 888, 853
NMR data are in accordance with literature values.[67]

### *3-Benzyl-2,2,4,4-tetramethylpentan-3-ol (2.29)*




**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.43-7.18 (m, 5H), 3.06 (s, 2H), 1.50 (s, 1H, OH), 1.17 (s, 18H)

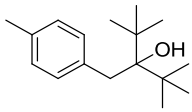
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 139.8, 131.4, 128.1, 125.9, 80.1, 42.8, 38.5, 29.4

**IR:** $\nu_{max}$ (film) 3598, 3085, 3061, 2959, 2916, 2878, 1493, 1481, 1452, 1393, 1086, 1001 $cm^{-1}$

**HRMS** (ESI) calcd. for $C_{16}H_{26}O$ $[M+Na]^+$ m/z 257.1876, found 257.1875

$^{1}$H NMR data are in accordance with literature values.[68]

### *2,2,4,4-Tetramethyl-3-(p-methylbenzyl)pentan-3-ol*

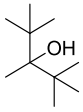



**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.32 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 3.06 (s, 2H), 2.40 (s, 3H), 1.21 (s, 18H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 136.5, 135.6, 131.7, 129.0, 80.1, 43.0, 38.2, 29.7, 21.3

**HRMS** (ESI) calcd for $C_{17}H_{28}O$ $[M+Na]^+$ m/z 271.2032, found 271.2032

### *2,2,3,4,4-Pentamethylpentan-3-ol (2.21)*




**Mp** 39–41 °C, lit.[69] 39–41 °C

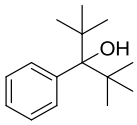
**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 1.26 (s, 1H, OH), 1.14 (s, 3H), 1.05 (s, 18H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 79.5, 41.1, 28.8, 21.7

**IR:** $\nu_{max}$ (film) 3506, 2983, 2960, 2916, 2876, 1371, 1106, 1065 $cm^{-1}$

NMR data are in accordance with literature values.[70]

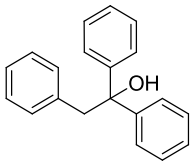
### *2,2,4,4-Tetramethyl-3-phenylpentan-3-ol*




Bromobenzene (3.0 mL, 29 mmol) was added dropwise to a suspension of lithium metal (500 mg, 72 mmol) in dry $Et_2O$ (20 mL) under an argon atmosphere. The concentration was measured to 1.39 M by the phenolphthalein titration method. The phenyllithium solution, thus obtained, was added dropwise to 2,2,4,4-tetramethylpentan-3-one (1.24 g, 8.7 mmol) under an argon atmosphere and stirred for 10 minutes. The mixture was diluted with $Et_2O$ and quenched with $H_2O$. The organic layer was separated and washed with saturated aqueous $NH_4Cl$ and $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated. No further purification was needed.

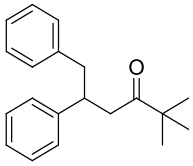
**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.77-7.72 (m, 1H), 7.64-7.58 (m, 1H), 7.41-7.33 (m, 1H), 7.29-7.23 (m, 2H), 1.98 (s, 1H, OH), 1.15 (s, 18H)
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 145.6, 128.1, 127.6, 127.4, 126.0, 125.8, 83.2, 41.7, 29.8
**IR:** $\nu_{max}$ (film) 3624, 3057, 2961, 2913, 2877, 1483, 1392, 1370, 1053 $cm^{-1}$
NMR data are in accordance with literature values.[71]

### *1,1,2-Triphenylethan-1-ol*




**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.45-6.95 (m, 13H), 6.95-9.89 (m, 2H), 3.56 (s, 2H), 2.23 (s, 1H, OH)
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 146.7, 135.9, 131.0, 128.2, 127.0, 126.3, 78.0, 48.1
**IR:** $\nu_{max}$ (film) 3548, 3086, 3060, 3027, 2956, 2910, 2856, 1492, 1446, 1199 $cm^{-1}$
**HRMS** (ESI) calcd for $C_{20}H_{18}O$ $[M-H_2O+H]^+$ m/z 257.1325, found 257.1325
NMR data are in accordance with literature values.[72]

### *2,2-Dimethyl-5,6-diphenylhexan-3-one (2.40)*




**Mp** 82–84 °C

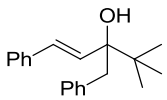
**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.39–6.96 (m, 10H), 3.52 (quint, *J* = 7.2 Hz, 1H), 3.02–2.81 (m, 3H), 2.74 (dd, *J* = 17.2, 6.3 Hz, 1H), 1.00 (s, 9H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 214.4, 144.5, 140.1, 129.3, 128.4, 128.2, 127.8, 126.4, 126.1, 44.2, 42.7, 42.7, 42.6, 26.2

**IR:** $\nu_{max}$ (neat) 3024, 2969, 2919, 1694, 1601, 1494, 1452, 1366, 1073 $cm^{-1}$

**HRMS** (ESI) calcd for $C_{10}H_{24}O$ $[M+H]^+$ m/z 281.1905, found 281.1905

### *(E)-3-Benzyl-4,4-dimethyl-1-phenylpent-1-en-3-ol 2.39*




**Mp** 103–105 °C

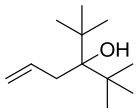
**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.41–7.06 (m, 10H), 6.41 (d, *J* = 16.0 Hz, 1H), 6.19 (d, *J* = 16.0 Hz, 1H), 3.03 (d, *J* = 13.1 Hz, 1H), 2.97 (d, *J* = 13.0 Hz, 1H), 1.35 (s, 1H, OH), 1.09 (s, 9H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 137.5, 137.0, 134.0, 131.1, 129.6, 128.6, 128.2, 127.2, 126.7, 126.42, 79.2, 41.8, 38.4, 25.9

**IR:** $\nu_{max}$ (neat) 3560, 3025, 2966, 2937, 2909, 2872, 1493, 1454, 1393, 1359, 1203, 1105, 1069, 1010 $cm^{-1}$

**HRMS** (ESI) calcd for $C_{10}H_{24}O$ $[M+H]^+$ m/z 281.1905, found 281.1900

### *3-Allyl-2,2,4,4-tetramethylpentan-3-ol*



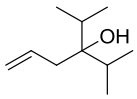
**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 5.93 (ddt, J = 17.5, 10.2, 7.5 Hz, 1H), 5.18-5.00 (m, 2H), 2.45 (d, *J* = 7.5 Hz, 2H), 1.55 (s, 1H, OH), 1.05 (s, 18H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 137.3, 118.7, 78.9, 42.4, 38.0, 28.9

**IR:** $\nu_{max}$ (film) 3581, 3076, 2960, 2918, 2878, 1482, 1392, 1370, 1001 $cm^{-1}$

NMR data are in accordance with literature values.[73]

### *3-Allyl-2,4-dimethylpentan-3-ol*



**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 5.85 (ddt, *J* = 17.5, 10.1, 7.4 Hz, 1H), 5.11–5.00 (m, 2H), 2.28 (dt, *J* = 7.4, 1.3 Hz, 2H), 1.89 (sept, *J* = 6.9 Hz, 2H), 1.26 (s, 1H, OH), 0.92 (d, *J* = 6.9 Hz, 12H)

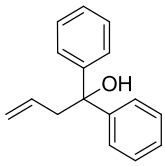
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 135.2, 117.7, 76.9, 38.4, 34.2, 17.6, 17.4

**IR:** $\nu_{max}$ (film) 3500, 3077, 2964, 2880, 1468, 1385, 991 $cm^{-1}$

**HRMS** (ESI) calcd for $C_{10}H_{20}O$ $[M-H_2O+H]^+$ m/z 139.1481, found 139.1482

$^{1}$H NMR data are in accordance with literature values.[74]

### *1,1-Diphenylbut-3-en-1-ol*



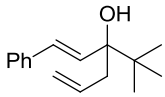
**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.61-7.53 (m, 4H), 7.45-7.28 (m, 6H), 5.78 (ddt, J = 17.2, 10.1, 7.2 Hz, 1H), 5.40-5.22 (m, 2H), 3.18 (d, *J* = 7.2 Hz, 2H), 2.75 (s, 1H, OH)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 146.5, 133.5, 128.2, 126.9, 126.0, 120.4, 76.9, 46.7

**IR:** $\nu_{max}$ (film) 3554, 3475, 3059, 3025, 2978, 2923, 1493, 1446, 1345, 1166, 990 $cm^{-1}$

NMR data are in accordance with literature values.[73]

### *(E)-3-(t-Butyl)-1-phenylhexa-1,5-dien-3-ol*




**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.46–7.16 (m, 5H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 5.89–5.67 (m, 1H), 5.20-5.17 (m, 1H), 5.16-5.12 (m, 1H), 2.66–2.51 (m, 1H), 2.40 (dd, *J* = 13.5, 9.3 Hz, 1H), 1.74 (s, 1H, OH), 1.25 (m, 9H)

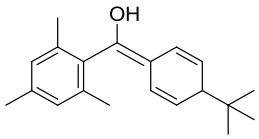
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 137.3, 134.6, 133.5, 129.5, 128.7, 127.3, 126.5, 119.7, 78.2, 40.1, 38.1, 25.7

**IR:** $\nu_{max}$ (film) 3554, 3079, 3060, 3026, 2958, 2873, 975 $cm^{-1}$

**HRMS** (ESI) calcd for $C_{16}H_{22}O$ $[M-H_2O+H]^+$ m/z 213.1638, found 213.1638

NMR data are in accordance with literature values.[75]

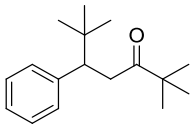
### *(4-(t-butyl)cyclohexa-2,5-dien-1-ylidene)(mesityl)methanol (2.45)*




**$^{1}$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$) 6.90 (s, 2H), 6.83 (dt, *J* = 10.3, 1.7 Hz, 1H), 5.86 (ddd, *J* = 10.3, 4.4, 1.9 Hz, 1H), 5.64 (dt, *J* = 10.3, 1.6 Hz, 1H), 5.54 (ddd, *J* = 10.3, 4.2, 1.9 Hz, 1H), 4.01 (s, 1H), 2.80 (tt, *J* = 4.3, 1.5 Hz, 1H), 2.21 (s, 3H), 2.16 (s, 3H), 2.11 (s, 3H), 0.84 (s, 9H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$) 144.4, 138.6, 137.8, 137.5, 132.7, 128.5, 128.4, 127.0, 125.4, 125.2, 122.0, 110.9, 48.9, 35.9, 27.4, 21.3, 19.6, 19.6

### *2,2,6,6-Tetramethyl-5-phenylheptan-3-one (2.46)*



**Mp** 99–100 °C, lit.[76] 100–101 °C

**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.25–7.10 (m, 5H), 3.09–3.15 (m, 2H), 2.71 (dt, *J* = 10.8, 8.9, 8.9 Hz, 1H), 1.01 (s, 9H), 0.88 (s, 9H)

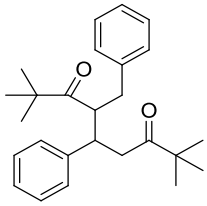
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 214.4, 143.0, 129.4, 127.6, 126.1, 50.4, 44.4, 37.9, 33.7, 28.4, 26.5

**MS** m/z 246 [$M^+$]

**IR:** $\nu_{max}$ (neat) 2959, 2915, 2867, 1699, 1472, 1365, 1342 $cm^{-1}$

$^{13}$C NMR data are in accordance with literature values.[77]

***4-Benzyl-2,2,8,8-tetramethyl-5-phenylnonane-3,7-dione (2.47)***



Isolated as a 3:1 diastereomeric mixture.

For the major diastereomer:

**Mp** 94–95 °C

**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.07–7.35 (m, 8H), 6.90–6.93 (m, 2H), 3.76 (dt, *J* = 6.7, 4.5 Hz, 1H), 3.44 (ddd, *J* = 11.1, 4.5, 3.3 Hz, 1H), 3.11 (d, *J* = 6.7 Hz, 2H), 2.94 (dd, *J* = 12.6, 11.1 Hz, 1H), 2.71 (dd, *J* = 12.6, 3.3 Hz, 1H), 1.10 (s, 9H), 0.74 (s, 9H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 217.2, 213.7, 143.5, 140.0, 129.4, 128.6, 128.3, 128.1, 126.8, 126.3, 54.0, 44.7, 44.2, 41.1, 35.9, 34.0, 26.6, 26.0

**IR:** $\nu_{max}$ (neat) 3062, 3027, 2968, 1707, 1682, 1476, 1454, 1364 $cm^{-1}$

**HRMS** (ESI) calcd for $C_{26}H_{34}O_2$ $[M+Na]^+$ m/z 401.2451, found 401.2452; HRMS (ESI) calcd for $C_{26}H_{34}O_2$ $[M+H]^+$ m/z 379.2632, found 379.2633.

**For the minor diastereomer:**

**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 7.25–7.02 (m, 8H), 6.97–6.84 (m, 2H), 3.56 (ddd, *J* = 9.1, 7.4, 5.1 Hz, 1H), 3.49–3.37 (ddd, *J* = 10.0, 6.7, 3.4 Hz, 1H), 3.10 (dd, *J* = 17.2, 10.0 Hz, 1H), 2.77–2.46 (m, 3H), 0.92 (s, 9H), 0.68 (s, 9H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) 219.0, 213.2, 142.4, 139.6, 129.3, 128.5, 128.4, 128.4, 126.8, 126.5, 52.9, 44.8, 44.2, 43.4, 39.8, 38.2, 26.3, 26.2.

# Chapter 3: Ring-opening of cyclic ethers by Grignard reagents

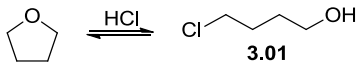
## 3.1 Background

The background for the project described in this chapter is an overlapping field of two subjects: The Grignard addition reaction and cleavage of cyclic ethers. The former reaction has already been described in chapter 2 and therefore the introduction to this chapter will mainly focus on the subject of ether cleavage.

### 3.1.1 Cyclic ether cleavage

***Protic cyclic ether cleavage***

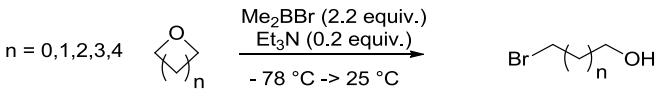
It is well-known that THF is labile under acidic conditions. By heating THF in HCl the corresponding chloro alcohol **3.01** can be formed (Scheme 19).[78] The reverse reaction occurs above 85 °C making **3.01** difficult to distill. In the same manner, the bromo alcohol can be formed.[79] The iodo alcohol can also be obtained although in a low yield.[80]




**Scheme 19 - Acidic cleavage of THF**

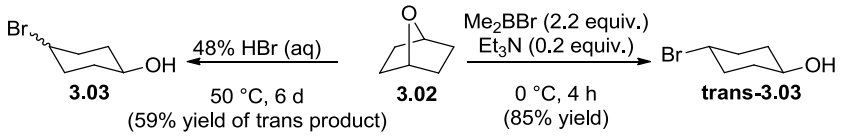
***Guindon's dimethylboron bromide conditions***

Guindon *et al.* have discovered mild conditions for cleaving ethers of various ring sizes by the use of dimethylboron bromide (Scheme 20).[81,82] The cleavage of the C-O bond occurs in a $S_N2$ fashion and forms the corresponding bromo alcohols in excellent yields.



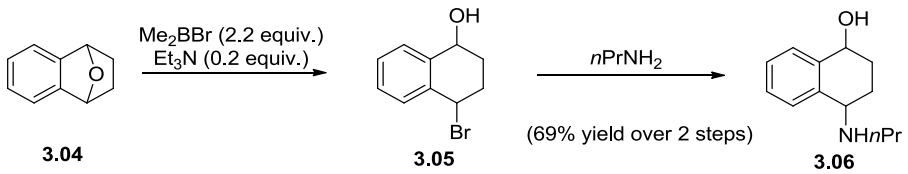

**Scheme 20 - Cyclic ether cleavage with dimethylboron bromide**

The regioselectivity have been demonstrated by the treatment of 2-methyltetrahydrofuran (MHF) with $Me_2BBr$ where the dominant product is 5-bromopentan-2-ol. Another advantage in this procedure is that the mild aprotic conditions applied offer a high level of control. Opening of the bicyclic ether 7-oxabicyclo[2.2.1]heptane **3.02** only produces *trans*-4-bromocyclohexanol (**3.03**) whereas the protic aqueous HBr treatment produces a *cis*/*trans*-mixture of **3.03** after 6 days at 50 °C (Scheme 21).[83]




**Scheme 21 - Ring opening of 7-oxabicyclo[2.2.1]heptane**

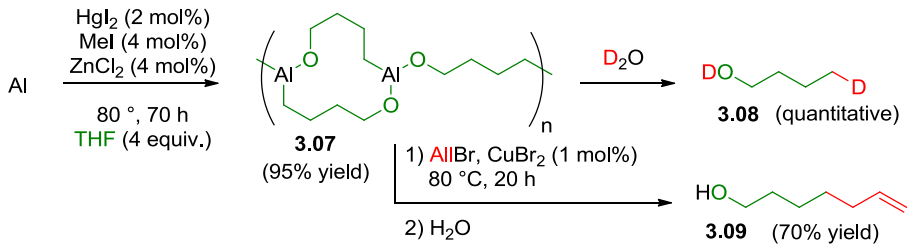
Furthermore, otherwise unstable compounds can be prepared by this protocol for synthetic applications. Oxabicycle **3.04** can be used to prepare bromotetraline **3.05** under these conditions where the protic conditions will afford naphthalene instead (Scheme 22).[84] Bromotetraline **3.05** is reported to be stable enough to undergo substitution with an amine.[84]




**Scheme 22 - Synthetic application**

### *Polymeric alkoxyalkylaluminum compounds*

A catalytic system was developed by Sumitani *et al.* to prepare alkoxyalkylaluminum compounds from the cleavage of cyclic ethers.[85] The optimal system is however not very benign as the catalyst component consists of $HgI_2$/MeI/$ZnCl_2$ in a 1:2:2 ratio and the reaction requires 70 hours at 80 °C (Scheme 23). The yield is excellent and the ratio of aluminum to 1-butanol is 2:3.

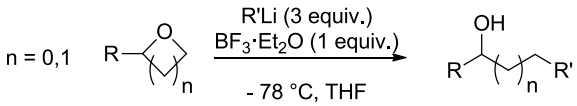



**Scheme 23 - Formation and application of alkoxyaluminum compound 3.07**

In THF, the carbons attached to the oxygen are electrophilic but when the carbons are bound to aluminum they are nucleophilic. This nucleophilicity has been demonstrated by deuterolysis of compound **3.07**. Deuterium is observed in the terminal positions in the product **3.08**. Furthermore, allylation into **3.09** is achieved by treatment of **3.07** with allylbromide using copper catalysis.

### 3.1.2 Boron trifluoride promoted ether cleavage using organolithium reagents

It is also possible to make a nucleophilic attack with a carbon nucleophile while cleaving ethers. For instance, the ring-opening have been reported by using organolithium reagents and $BF_3{\cdot}Et_2O$ by Eis *et al.*[86] The useful electrophiles are various substituted epoxides and oxetanes. The nucleophiles are aliphatic and aromatic organolithium compounds and a large excess is applied (Scheme 24). The yields are based on the cyclic ether and are excellent. The alkylation rate of THF is slow and only results in a low yield of 20%.




**Scheme 24 - Boron trifluoride etherate promoted organolithium additions**

In the absence of $BF_3{\cdot}Et_2O$, no cyclic ether alkylation occurs and at least one equivalent of $BF_3{\cdot}Et_2O$ is needed as substituted fluoroboranes are not reactive intermediates. This is determined from experiments showing that neither $n$BuBF$_2$ nor $n$Bu$_2$BF in the absence of $BF_3$ converts any of the cyclic ethers. The mechanism is

suggested to be initiated by coordination of $BF_3$ to the endocyclic oxygen in ether **3.10** (Figure 17, **A**). The organolithium reagent then performs a nucleophilic attack on the electrophilic carbon in **3.10**, giving intermediate **3.11**. This intermediate undergoes attack by alkyl lithium to finally produce tetraalkyl borate **3.13** and lithium alkoxide **3.12**.

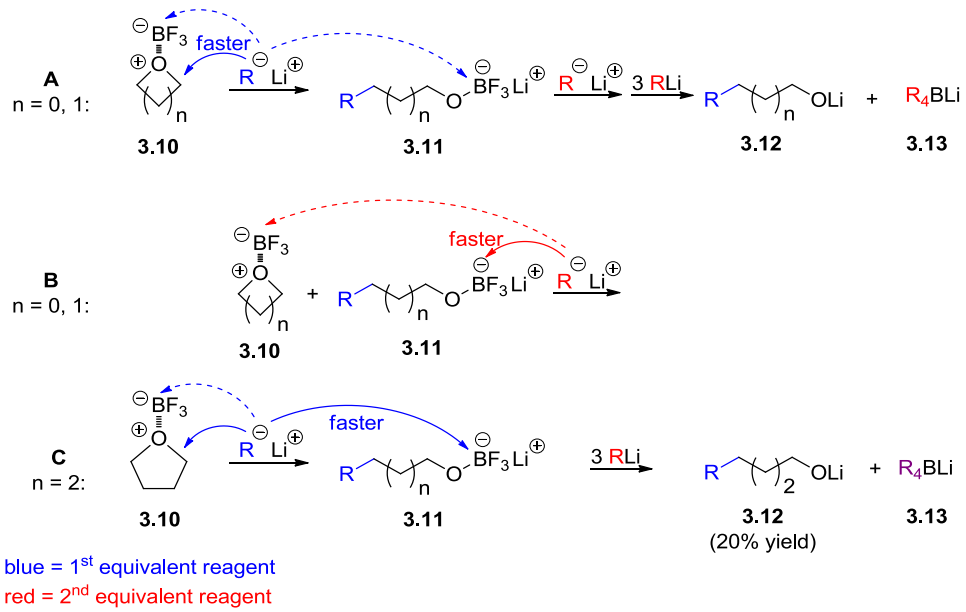



**Figure 17 - Suggested mechanism for the borontrifluoride etherate promoted organolithium addition**

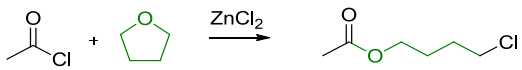
While the reaction progress, a mixture of **3.10** and **3.11** are in the solution and when comparing the reaction to the boron, the nucleophilic attack in compound **3.11** is faster than the attack in compound **3.10** (Figure 17, **B**). Therefore, the low yields from tetrahydrofurans are not from the reaction of the organolithium with boron on **3.10**.

They postulate that the success of the reaction instead relies on the rate of addition by the organolithium reagent to the electrophilic carbon in **3.10** being faster than the addition to the boron complex **3.11** (Figure 17, blue arrows). This seems to be the case for the epoxides and the oxetane but not the tetrahydrofurans. The low yield in the tetrahydrofurans originates from the borane compounds consuming the organolithium compounds (Figure 17, **C**).

Later, Chou *et al.* have found the cleavage of five- and six-membered rings possible with organolithium reagents in the presence of one equivalent $BF_3{\cdot}Et_2O$.[87] For the reaction of *n*BuLi with THF, 1-octanol is isolated in 55% yield. The reaction of *n*BuLi with MHF was also found to be regioselective as 2-nonanol is isolated as the sole product. The reaction of *n*BuLi with tetrahydropyran (THP) results in a lower yield and higher temperatures are needed compared to the reaction with THF.

### 3.1.3 Reaction of ethers with acids, acid chlorides and acid anhydrides

Zinc or ferric chloride has for a long time been known to catalyze the cleavage of ethers by acetyl chloride in the formation of esters (Scheme 25).[88–91] This also works for carboxylic acids and acid anhydrides.[92] Other Lewis acids that catalyzes this reaction are $Zn(OTf)_2$,[91] Zn dust,[93] $Fe(CO)_5$,[94] $MgBr_2$,[95] $BBr_3$,[96] $BCl_3$[97], NaI,[98] $I_2$,[99] $AlCl_3$-NaI,[100] $InBr_3$,[101] $BiCl_3$,[102,103], $Ln(NO_3)_3{\cdot}6H_2O$,[104] $Bi(NO_3)_3{\cdot}5H_2O$,[105] $MoCl_5$,[106] $WCl_6$,[106] $WBr_5$,[106] $NbCl_5$,[106] $TaCl_5$,[106] arenetricarbonylmetal complexes,[107] and other rare earth metal compounds.[108] Still, zinc-salts are preferred because they are abundant, cheap and have a low toxicity.




**Scheme 25 - Zinc catalyzed ether cleavage by acetyl chloride**

Based on their findings, Enthaler and Weidauer recently suggested the mechanism for the zinc triflate catalyzed reaction to be as depicted in Figure 18.[91] Initially THF is coordinated to zinc forming complex **3.14**. Upon addition of the acid chloride, one THF molecule dissociates and the acid chloride is coordinated into **3.15**. By zinc coordination, the oxygen and the adjacent carbon are both activated, allowing the chloride attack on carbon while the C-O bond is being cleaved. The chloroester dissociates and the zinc complex **3.14** is ready for another cycle.

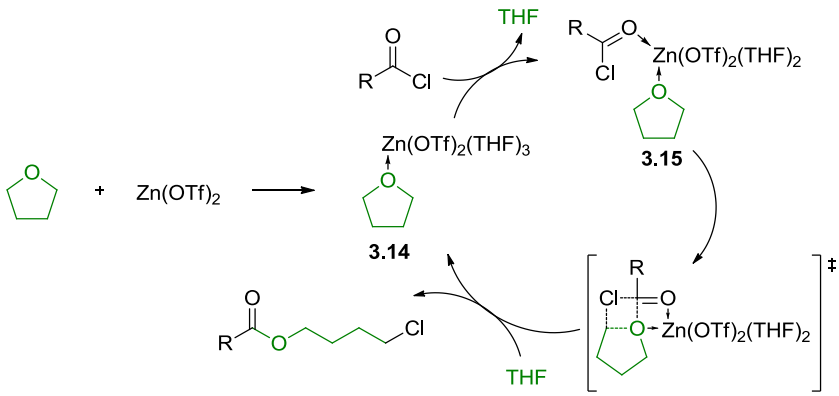
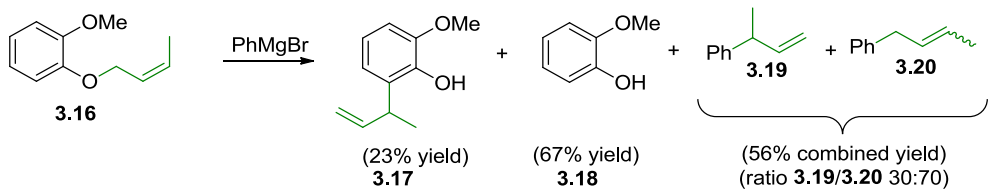



**Figure 18 - Mechanism of zinc catalyzed ether cleavage by acetyl chloride**

### 3.1.4 Cleavage of allyl and benzyl ethers by Grignard addition

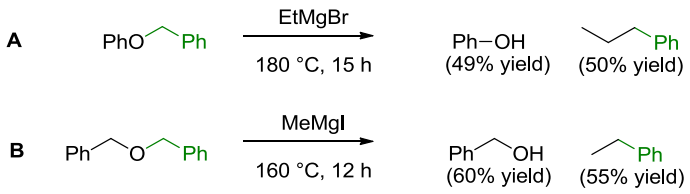
Allyl ethers are readily cleaved by Grignard reagents.[109,110] The reaction of *o*-methoxyphenylcrotyl ether **3.16** and phenylmagnesium bromide produces the Claisen rearrangement product **3.17** in 23% yield and phenol **3.18** in 67% yield (Scheme 26). The latter product originates from cleavage of the allyl ether and the addition of phenylmagnesium bromide occurs by following both an $S_N2$ (like Figure 7, Page 11) and an $S_N2'$ mechanism.[111]




**Scheme 26 - Reaction of *o*-methoxyphenyl crotyl ether and phenylmagnesium bromide**

The reaction works for various allyl ethers, including the diallyl ethers, and Grignard reagents in moderate yields.[112–114] Kharasch and Huang have found the cleavage of benzyl alkyl, benzyl aryl, aryl allyl, and diaryl ethers possible by Grignard reagents in the presence of $CoCl_2$ at room temperature.[115] In these reactions no addition of the Grignard reagent is observed. For instance, phenylbenzyl ether in the presence of $CoCl_2$ gives phenol and toluene and phenylallyl ether affords phenol and propylene.

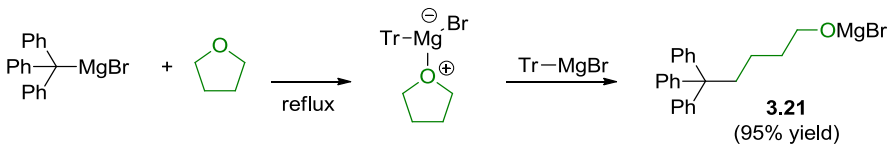
Addition of the Grignard reagent have been reported to be possible on benzyl ethers although this requires a much higher temperature (Scheme 27).[116]




**Scheme 27 - Grignard addition on benzylic ethers**

### 3.1.5 Cleavage of THF by tritylmagnesium bromide

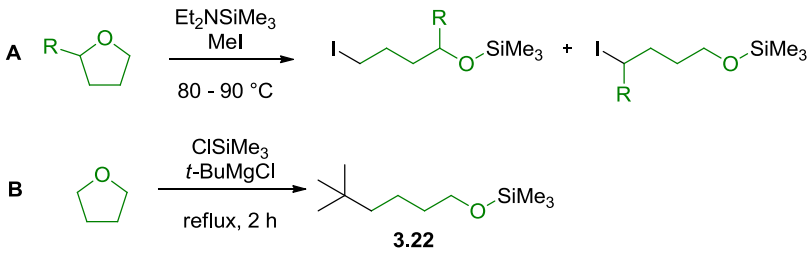
Though the cleavage of THF have not been generally found to occur with Grignard reagent it is reported that tritylmagnesium bromide is able to perform the transformation since refluxing this solution in THF produces 5,5,5-triphenylpentan-1-ol (**3.21)** in an excellent yield (Scheme 28). Tritylmagnesium bromide is highly ionized in solution which is not the case for most other Grignard reagents. As the size of the trityl group is large, the Schlenk equilibrium should lie towards the monoalkylmagnesium compound and the concentration of $MgBr_2$ in solution should be low. The complexation agent is therefore thought to be tritylmagnesium bromide although the possibility of magnesium bromide fulfilling this role cannot be excluded.




**Scheme 28 - Cleavage of THF by tritylmagnesium bromide**

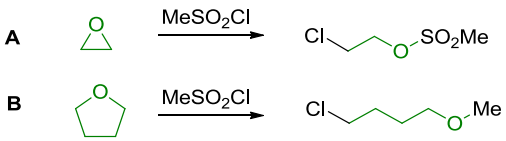
### 3.1.6 Other ether cleaving reactions

4-Halobutyltrialkylsilyl ethers have been prepared by cleavage of THF by using the corresponding *in situ* generated trialkylsilyl halides (Scheme 29, **A**).[117] In a similar system, *t*-butylmagnesium chloride attacks the electrophilic carbon instead of the chloro silane forming compound **3.22** (Scheme 29, **B**).[118]




**Scheme 29 - Halosilylation of cyclic ethers**

The reaction of methanesulfonyl chloride with various epoxides produced the corresponding chloroalkylmethyl sulfites (Scheme 30, **A**).[119] The same reagent on THF produced the corresponding 4-chlorobutyl alkyl ethers instead (Scheme 30, **B**).




**Scheme 30 - The reaction of methanesulfonyl chloride on ethylene oxide and THF**

### 3.1.7 Microwave irradiation

In general, heating of organic reactions have mostly been performed by using oil baths, sand baths or heating jackets. These traditional techniques are slow and a temperature gradient can be developed within the reaction mixture as the heating comes from the external surface. Furthermore, local overheating can lead to decomposition of the compounds in the mixture. By the aid of microwave irradiation with an external field, the microwave energy is absorbed by the solvent or reactants and not the reaction vessel itself.[120] If the apparatus is properly designed, the temperature increase in the mixture will be uniform and in a pressurized system it is possible to reach temperatures far above the boiling point of the solvent used.

From a mechanistic point of view, microwave irradiation can be divided into an electric field component and a magnetic field component. The former is responsible for the dielectric heating via two mechanisms: the dipolar polarization mechanism and the conducting mechanism. A substance must have a dipole moment to be able

to generate heat when irradiated with microwaves. In the dipolar polarization mechanism the heating occurs when the dipole will attempt to align itself with the external electric field by rotation. Water, which has large dipole moment (dielectric constant, $\varepsilon_{25\ °C}$ = 80), is easily heated, while dioxane lacks a dipole moment ($\varepsilon_{25\ °C}$ = 2.3) and is therefore unable to be heated by microwave irradiation.

The conduction mechanism is explained with a solution containing ions. The ions will move through the solution under the influence of an electric field. By this movement, kinetic energy is converted into heat from the increased collision rate in the solution. The conductivity mechanism is a much stronger interaction than the dipolar mechanism.

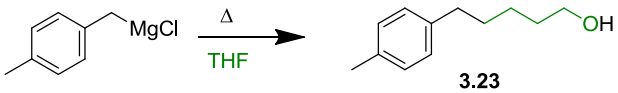
The ability of different solvents to generate heat also depends on the solvents loss angles, which is a factor that represents the dielectric materials ability to store electrical potential energy under the influence of an electric field. For instance, if two solvents with similar dielectric constants are radiated with the same radiation power for the same time, the final temperature would be higher for the solvent with a higher loss angle.

The dielectric constant of any solvent decreases whenever the temperature of the solvent increases. For instance, the dielectric constant for $H_2O$ decreases from 80 at room temperature to 20 at 300 °C and therefore behaves as a pseudo-organic solvent.

### 3.1.8 Project idea

The background in chapter 3 focuses on the cleavage of ethers. No efficient 1-step protocol exists where a carbon-carbon bond is formed together with the unprotected alcohol, by using tetrahydrofuran as the electrophile.

As described in section 2.2.1, heating a Grignard reagent in THF resulted in ring-opening of the cyclic ether and addition of the nucleophile to **3.23** in a high yield (Scheme 31).




**Scheme 31 - Cleavage of THF by the reaction with *p*-methylbenzylmagnesium chloride**

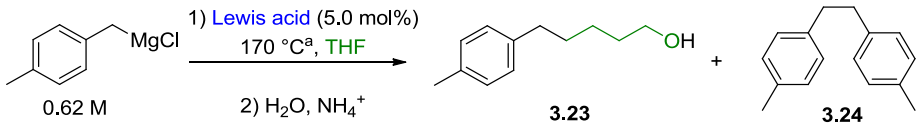
This discovery encouraged us to further develop this reaction. However, the reaction conditions required optimization. Temperature, reaction time, catalyst and co-solvent are some of the parameters which ought to be adjusted. Furthermore the scope of the reaction will be investigated by changing the reagents and ethers.

## 3.2 Results and discussion

### 3.2.1 Optimization of reaction conditions by conventional heating

Based on the analysis of the obtained GC-MS chromatogram from the retro-Grignard addition project the reaction was slow but clean as no other side product was observed in significant amount. A test reaction at 140 °C for 10 days gave almost complete conversion according to the chromatogram. Initially, we were interested in determining whether adding an additional Lewis acid, other than the one from the Grignard reagent, could catalyze the reaction. These screening reactions were performed in a sealed tube using a silicone oil bath as the heating source and the results are depicted in Table 7.

**Table 7 - Grignard addition and ring opening by silicone oil bath heating. Screening for a catalyst**



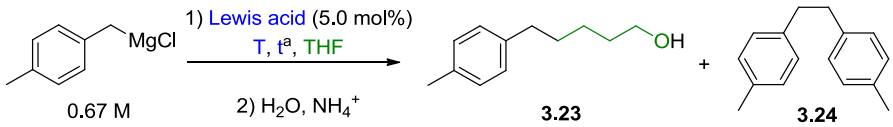

| Entry | Lewis acid | T (h) | Yield **3.23**[b] | Yield **3.24**[b] |
|---|---|---|---|---|
| 1 | - | 21 | 6% | -[c] |
| 2 | $CuBr_2$ | 17 | 10% | -[c] |
| 3 | $CuBr_2$ | 43 | 22% | 12% |
| 4 | $AlCl_3$ | 43 | 6% | 4% |
| 5 | $MgBr_2{\cdot}Et_2O$ | 40 | 19% | 5% |
| 6 | $TiCl_4$ | 40 | 0% | 20% |
| 7 | CuBr | 44 | 22% | 8% |
| 8 | $FeCl_3$ | 44 | 20% | 9% |
| 9 | $InCl_3$ | 44 | 8% | 7% |
| 10 | $FeCl_2$ | 44 | 21% | 10% |

a) Heated in sealed vessel by silicon oil bath. b) Isolated yield based on basetiter concentration. c) Yield not determined

The yields in these reactions were rather low, but it seems in some cases that the additional Lewis acid might have a catalytic effect. Copper salts seemed to be a good choice (Table 7, entry 2, 3 and 7). Titanium (IV) chloride catalyzes the dimerization reaction instead (Table 7, entry 4).

Silicone oil was inconvenient to work with and for easier handling an aluminum block was ordered from the work shop. In the following results, heating was performed in this aluminum block. These results are depicted in Table 8.

**Table 8 - Grignard addition and ring opening by aluminum block heating. Screening for a catalyst and the optimal temperature**




| Entry | Lewis acid | t (°C) | T (h) | Yield **3.23**[b] | Yield **3.24**[b] |
|---|---|---|---|---|---|
| 1 | - | 170 | 41 | 82% | 4% |
| 2 | CuI | 170 | 41 | 69% | 9% |
| 3 | - | 160 | 41 | 70% | 6% |
| 4 | $MgBr_2 \cdot Et_2O$ | 160 | 39 | 60% | 4% |
| 5 | $BiCl_3$ | 160 | 41 | 40% | 25% |
| 6 | - | 150 | 97 | 79% | nd[c] |
| 7 | - | 140 | 260 | 82% | 5% |
| 8 | $CuBr_2$ | 140 | 260 | 69% | 10% |

a) Heated in sealed vessel by aluminum block. b) Isolated yield based on basetiter concentration. c) not determined.

This change of setup dramatically increased the reaction rate. Interestingly, it now seems that additional Lewis acid lowers the yield of **3.23** and the Lewis acid instead increases the amount of bibenzylic product **3.24** formed (Table 8, entry 2, 5 and 8). In the reactions without non-magnesium based Lewis acids, the 5% yield of the bibenzylic compound **3.24** presumably originates from the formation of the Grignard reagent (Table 8, entry 1, 3, 4, 6 and 7). Bismuth was found to be a good catalyst for the dimerization process (Table 8, entry 5). It is known that metal compounds can

catalyze the formation of a bibenzylic compound though a stoichiometric amount of an oxidant is needed.[121,122]

It can be difficult to establish which species from the dimerization and the Schlenk equilibria that were the reactive species (Equation 1, Page 10). THF is favoring the Schlenk equilibrium but the addition of magnesium (II) bromide should shift the equilibrium towards the monomer. The rate of the reaction with added magnesium (II) bromide was a little bit lower (Table 8, entry 4) and supports the previous observations as the addition with magnesium (II) bromide lowers the reaction rate (Table 1, Entry 8, page 15).

A higher conversion rate might be obtained by using dibenzyl magnesium, but the synthesis of this suffers from practical difficulties. Traditionally, precipitation of $MgCl_2$ by the addition of dioxane shifts the Schlenk equilibrium, but only a low yield of 29% of $Bn_2Mg$ have been reported, from which the crystalline $Bn_2Mg(THF)_2$ complex is prepared in 55%.[123] The preparation of $Bn_2Mg(THF)_2$ have been improved to a yield of 71% from toluene and BnMgCl by Bailey *et al.*[124] The yield from the latter reaction is lower than the yield obtained from the addition of *p*-methylbenzylmagnesium chloride with THF. Therefore, experiments with this substrate were not pursued.

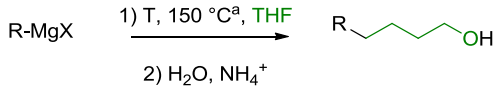
Under all the above reactions in Table 8, high pressure was developed and at 170 °C the screw cap from the reaction vial was not always able to withstand this and the cap may therefore break. Lower temperatures were then needed. This resulted in longer reaction times for the reaction that was already slow. The number of cap breaks were reduced when lowering the temperature to 160 °C and even further at 150 °C. At 140 °C around 11 days was needed to result in a high conversion (Table 8, entry 7 and 8).

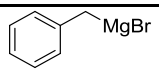
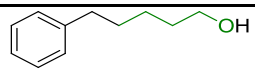
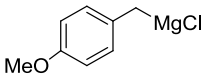
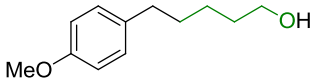
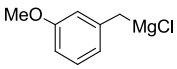
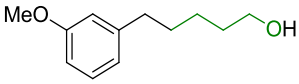
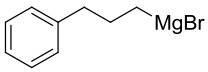
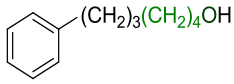
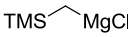
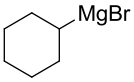
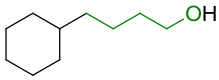
An approach to resolve this pressure problem was to perform the reaction in a Schlenk tube with an argon flow and use mesitylene as a cosolvent. This procedure unfortunately did not produce any Grignard addition ring opening product. The cause could be that THF was refluxing and were in the proximity of the Grignard reagent.

### 3.2.2 Substrate scope study with conventional heating

Following the optimization it was decided to perform a substrate scope study. For safety reasons the temperature was set to 150 °C, but the reactions then required longer reaction times. The screening results are depicted in Table 9.

**Table 9 - Grignard addition and ring opening by aluminum block heating. Grignard reagent scope**



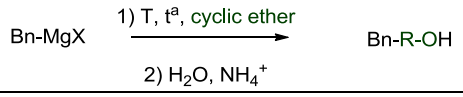

| Entry | substrate | [RMgX] (M) | T (h) | Product | Yield[b] |
|---|---|---|---|---|---|
| 1 |  | 0.49 | 114 |  | 61% |
| 2 |  | 0.26 | 95 |  | 40% |
| 3 |  | 0.25 | 97 |  | 61% |
| 4 |  | 0.77 | 233 |  | traces[c] |
| 5 |  | 1.19 | 235 | - | -[d] |
| 6 |  | 1.13 | 237 |  | traces[c] |

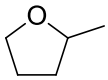
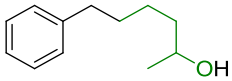
a) Heated in sealed vessel by aluminum block. b) Isolated yield based on basetiter concentration. c) Detected by GC-MS-analysis. Product not isolated. d) Addition product not detected.

The benzylic Grignard reagents resulted in a moderate yield (Table 9, entry 1-3). Primary and secondary alkyl Grignard reagents only resulted in trace amounts of the addition products (Table 9, entry 4-6).

A small screening of some cyclic ethers other than THF has also been performed as depicted in Table 10.

**Table 10 - Grignard addition and ring opening by aluminum block heating. Cyclic ether scope**




| Entry | [RMgX] (M) | cyclic ether | t (°C) | T (h) | Product | Yield[c] |
|---|---|---|---|---|---|---|
| 1 | 0.74 |  | 170 | 65 | - | -[c] |
| 2 | 0.98 |  | 160 | 163 |  | 23% |

a) Heated in sealed vessel by aluminum block. b) Isolated yield based on basetiter concentration. c) Addition product not detected.

The Grignard reagents were readily formed in these ether solvents and it was even possible to obtain a higher concentration when MHF was used. THF is miscible with water and the water solubility of MHF is between THF and diethyl ether. Addition and ring opening of THP was not observed (Table 10, entry 1) and the yield of the addition product with MHF was rather low after prolonged heating (Table 10, entry 2). MHF is commonly used when higher temperatures are needed compared to THF and therefore a higher temperature is also applied in the reaction. Unfortunately in this case, MHF was more stable which resulted in a slower reaction. It was believed that longer reaction times can give higher yields but this was not convenient.

### 3.2.3 Optimization of reaction conditions by microwave irradiation

At this point it was time for another equipment upgrade. A microwave reactor was now available and the numerous applications by this method can be exploited. Higher pressure was now achievable as the vial can withstand a pressure up to 20 bars. Higher temperature could safely be employed and another advantage by microwave heating was the ability to monitor the pressure development which indeed came in handy in this project.

The microwave apparatus was tested to the limit of 20 bars and the optimal condition applied for the ring opening reaction in THF. THF has a dielectric constant of 7.6 at

room temperature, though the Grignard reagents may have aided in the ionization of the solution, thereby making heating of the reaction by microwave irradiation possible. Performing the reaction at 180 °C for 24 hours were found to be the upper safe limit when only 3 mL was heated in a 10 mL microwave vial (normal reaction volume is 2-5 mL in 10 mL vials). After 16 hours, the reaction with *p*-methylbenzylmagnesium chloride and THF produced a decent yield of 60%, while 24 hours produced a yield of 75% (Table 11, entry 1-2). According to the microwave apparatus´s pressure monitoring system, the pressure in this case rose from 12.9 bar to 20.0 over these 24 hours (Figure 19).

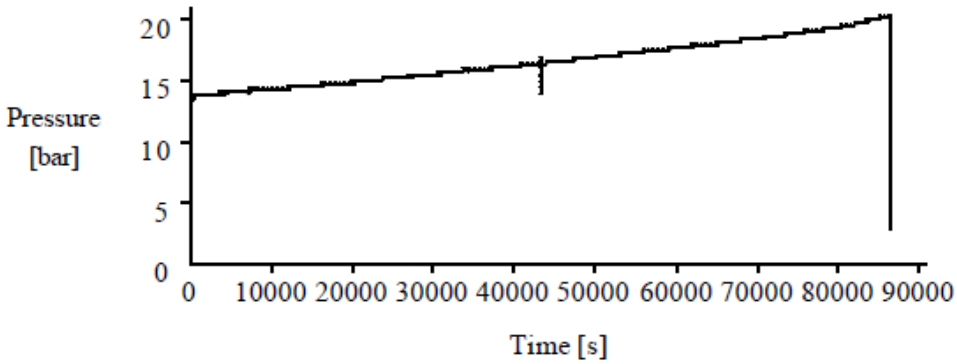
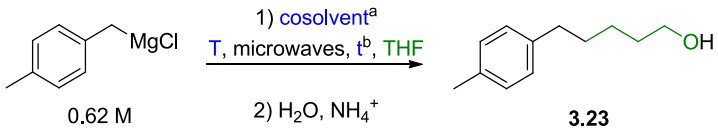



**Figure 19 - Ring opening by microwave irradiation. Pressure monitoring**

In the reaction, two molecules became one and the ether molecule was a gas at these conditions so in theory the pressure should be decreasing. The reason why the pressure instead was increasing in these reactions still remains a puzzle. An idea to circumvent the high pressure problem was to add an inert cosolvent to the reaction mixture with the possibility to raise the temperature and elucidate whether this can increase the rate of the reaction. The results of these experiments are depicted in Table 11.

**Table 11 - Ring opening by microwave irradiation. Cosolvent optimization**




| Entry | Cosolvent | Cosolvent bp. | t (°C) | T (h) | p (bar) | Yield[c] |
|---|---|---|---|---|---|---|
| 1 | - | - | 180 | 16 | 13.3-16.0 | 60% |
| 2 | - | - | 180 | 24 | 12.9-20.0 | 75% |
| 3 | Mesitylene | 165 | 180 | 16 | 11.2-14.0 | 36% |
| 4 | Decaline (rac.) | 187/196[d] | 180 | 16 | 11.0-13.0 | 40% |
| 5 | Decaline (rac.) | 187/196[d] | 190 | 16 | 12.5-15.0 | 44% |
| 6 | Decaline (rac.) | 187/196[d] | 200 | 16 | 15.2-18.5 | 49% |
| 7 | Tetraline | 207 | 200 | 16 | 14.5-18.0 | 48% |
| 8 | Benzylbenzene | 264 | 200 | 16 | 14.4-18.0 | (<58%)[e] |
| 9 | Bibenzyl | 284 | 200 | 16 | 14.6-20.5 | 60% |
| 10 | Bibenzyl | 284 | 180 | 24 | 11.0-13.9 | 54% |

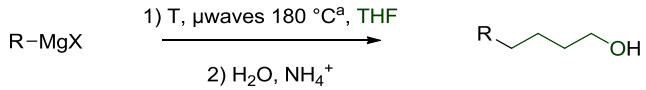
a) 2.5 mL Grignard reagent solution in THF and 0.5 mL or 0.5 g cosolvent. b) Heated in sealed vessel by microwave irradiation. c) Isolated yield based on basetiter concentration. d) Individual boiling point of *trans*-decaline 187 °C, *cis*-decaline 196 °C. e) 6,6-diphenylhexan-1-ol produced as byproduct

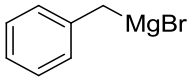
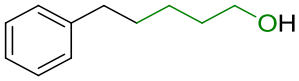
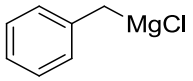
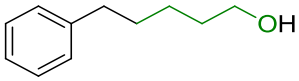
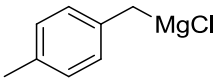
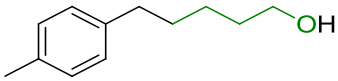
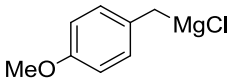
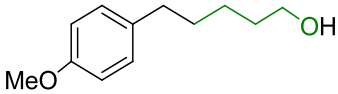
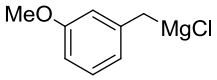
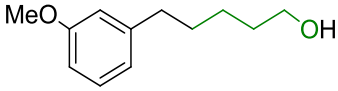
As expected the reactions without cosolvent were faster than the reactions with cosolvent at the same temperature. Using a high boiling cosolvent reduced the pressure, but not sufficiently to be able to raise the temperature to improve the yield within the same reaction time while simultaneously keeping the pressure at a safe level. No improvement was found by this optimization.

### 3.2.4 Substrate scope study by microwave irradiation

A short substrate scope investigation with microwave irradiation and in the absence of a cosolvent was performed and the results are depicted in Table 12.

**Table 12 - Grignard addition and ring opening by microwave irradiation. Grignard reagent scope**

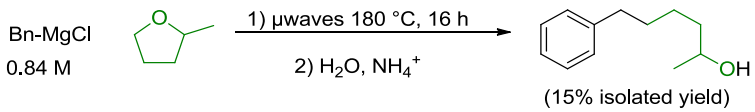



| Entry | substrate | [RMgX] (M) | T (h) | Product | Yield[b] |
|---|---|---|---|---|---|
| 1 |  | 0.49 | 16 |  | 65% |
| 2 |  | 0.68 | 16 |  | 86% |
| 3 |  | 0.62 | 24 |  | 75% |
| 4 |  | 0.41 | 24 |  | 35% |
| 5 |  | 0.26 | 20 |  | 68% |

a) Heated in sealed vessel by microwave irraditation. b) Isolated yield based on basetiter concentration.

The yields in the substrate screening were modest to good. Benzylmagnesium chloride resulted in a higher yield than benzylmagnesium bromide which supports the previous kinetic experiment where the benzylmagnesium chloride is shown to be more nucleophilic (Table 12, entry 1-2).

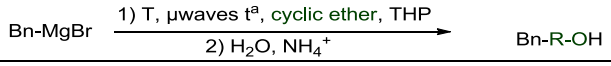
An attempt to ring-open THP failed as the microwave oven was unable to heat the less polar solvent up to the desired temperature. THP has a dielectric constant of 5.7 at room temperature[125] which is lower than the dielectric constant of THF. Another attempt was to use 1,2-dimethoxyethane (DME) as a cosolvent for making the reaction mixture more polar, but in this case the benzylmagnesium chloride reacted with DME instead. DME is known to make octahedral complexes with Grignard reagents.[126] A reaction of benzyl magnesium chloride with MHF was also performed and resulted in a low yield of 15% after 16 hours and the temperature or heating time could not be increased significantly due to the high pressure developed (Scheme 32).

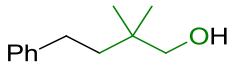
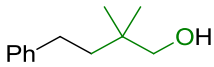
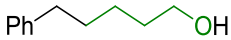
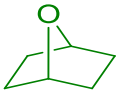
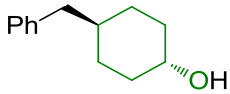
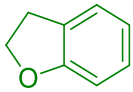
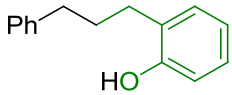
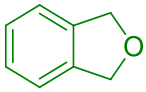
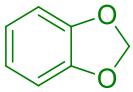
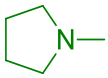
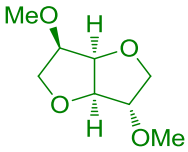



**Scheme 32 - Grignard addition and ring opening of MHF by µwave irradiation**

The inability of THP to undergo ring-opening by a Grignard reagent could be exploited. The Grignard reagent could be formed in THP and then be used to react with other cyclic ethers. Higher temperatures could be employed and by using this method another substrate screening has been performed as depicted on Table 13. In the successful experiments the yields were moderate. As expected the ring-opening of a four membered ring was much faster due to the increased ring-strain compared to the five membered rings (Table 13, entry 1-2). Ring-opening of THF in tetrahydropyran was also slower than in neat THF even at higher temperature and this result was an effect of dilution (Table 13, entry 3). 7-Oxabicyclo[2.2.1]heptane **3.02** opens readily and only resulted in the *trans*-product (Table 13, entry 4). This indicates that the reaction occurs in an $S_N2$ fashion. 2,3-Dihydrobenzofuran ring-opens but a problem existed in isolating the compound as another unidentified phenol was also formed (Table 13, entry 5). Surprisingly, phthalan did not ring-opened into the benzylic alcohol (Table 13, entry 6). 1,3-Benzodioxole actually performed two ether cleavage reactions as 1,3-diphenyl propane was formed as the major product and only traces of the mono-addition product were observed by GC-MS-analysis (Table 13, entry 7). No product was detected when the Grignard reagent was heated with *N*-methylpyrrolidine or dimethyl isosorbide (Table 13, entry 8-9).

**Table 13 - Grignard addition and ring opening by microwave irradiation. Cyclic ether reagent scope**

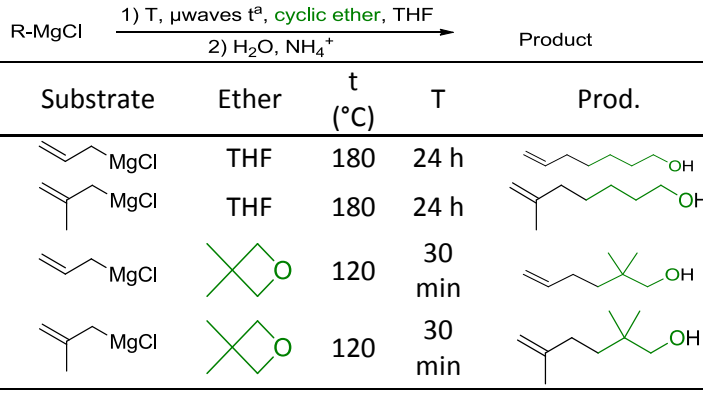



| Entry | [RMgBr] (M) | Cyclic ether | t (°C) | T (h) | Prod. | Yield[b] |
|---|---|---|---|---|---|---|
| 1 | 0.66 |  | 200 | 3 |  | 52% |
| 2 | 0.66 |  | 180 | 4 |  | 69% |
| 3 | 0.58 |  | 190 | 24 |  | 40% |
| 4 | 0.66 |  | 200 | 25 |  | 44% |
| 5 | 0.66 |  | 200 | 24 |  | 49% |
| 6 | 0.66 |  | 200 | 20 | - | -[c] |
| 7 | 0.75 |  | 200 | 20 | - | traces[d] |
| 8 | 0.66 |  | 200 | 20 | - | -[c] |
| 9 | 0.78 |  | 200 | 24 | - | -[c] |

a) Heated by microwave irradiation, 2.5 mL Grignard reagent solution in THP and 0.5 mL cyclic ether. b) yield based on basetiter concentration. c) Product not detected. d) GC-MS-analysis show that 1,3-diphenyl propane was formed as the major product (not isolated).

Allylic Grignard reagents are also able to make this transformation (Table 14).

**Table 14 - Grignard addition and ring opening by microwave irradiation. Allylic reagents**




| Entry | [RMgCl] (M) | Substrate | Ether | t (°C) | T | Prod. | Yield[b] |
|---|---|---|---|---|---|---|---|
| 1 | 2.3 M | | THF | 180 | 24 h | | 79% |
| 2 | 0.48 M | | THF | 180 | 24 h | | 50% |
| 3 | 2.3 M | | | 120 | 30 min | | 84% |
| 4 | 0.48 M | | | 120 | 30 min | | 67% |

a) Heated by microwave irradiation, 2.5 mL Grignard reagent solution in THP and 0.5 mL cyclic ether. b) Yields are based on basetiter concentration.

Although the allyl Grignard reagents generally are more reactive than the benzylic reagents in the nucleophilic additions to carbonyl, the two reagents required an equal amount of time in the addition and ring-opening of THF (Table 14, entry 1-2). For the opening of the 4-membered ring, the reaction was much faster and could be performed at a much lower temperature (Table 14, entry 3-4). The yields were again modest to good in these reactions. No further experiments with the allyl Grignard reagents were performed as it was sufficient to establish that they function equally well or better than the benzylic Grignard reagents.

## 3.3 Conclusion

The addition of a Grignard reagent to THF was possible and optimization was performed by using *p*-methylbenzylmagnesium bromide in THF. Adding an additional Lewis acid did not improve the yield of the reaction. The most convenient way of heating was by microwave irradiation. Adding a cosolvent to lower the pressure in the reaction did not increase the yield of the reaction. A short scope study with Grignard reagents was performed. The study showed that allylic and benzylic Grignard reagents gave conversion of THF into their corresponding ring opened products while primary and secondary aliphatic Grignard reagents did not afford any of the desired products. A short scope study by reacting Grignard reagents with different cyclic ethers was carried out and resulted good yields for the cleavage of oxetanes, decent yields for the cleavage of some tetrahydrofurans and no conversion of tetrahydropyran.

## 3.4 Experimental

### 3.4.1 General methods

The same general methods as described in section 2.4.1 were followed. Furthermore, the allylic Grignard reagents were purchased from Sigma-Aldrich and used as received. The remaining Grignard reagents were prepared in a three-neck round-bottom flask by slow addition of the halide to a magnesium suspension in freshly distilled THF under an argon atmosphere. Microwave heating was performed with a Personal Chemistry Emry Optimizer reactor.

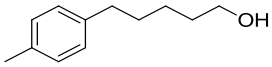
### 3.4.2 General procedure for the ring-opening reaction of THF by Grignard reagents with conventional heating

*p*-Methylbenzylmagnesium chloride (10.0 mL, 0.62 M in THF, 0.62 mmol) was added to a screw-top vial under argon atmosphere and the vial was sealed. The reaction mixture was heated by aluminum block at 170 °C for 41 hours. The mixture was cooled to ambient temperature, diluted with diethyl ether and the reaction was quenched with $H_2O$. The organic phase was washed with saturated aqueous $NH_4Cl$ and $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated. Column chromatography (EtOAc/heptane) furnished 5-(*p*-tolyl)pentan-1-ol **3.23** (907 mg, 5.24 mmol, 82%).

### 3.4.3 General procedure for the ring-opening reaction of THF by Grignard reagents with microwave irradiation

Benzylmagnesium chloride (4.0 mL, 0.68 M in THF, 2.72 mmol) was added to a microwave vial under argon atmosphere and the vial was sealed. The reaction mixture was heated by microwave irradiation at 180 °C for 16 hours. The mixture was cooled to ambient temperature, diluted with diethyl ether and the reaction was quenched with $H_2O$. The organic phase was washed with saturated aqueous $NH_4Cl$ and $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated. Column chromatography (EtOAc/heptane) furnished 5-phenylpentan-1-ol (384 mg, 2.34 mmol, 86%).

### *5-(p-tolyl)pentan-1-ol (3.23)*



***R*$_f$** = 0.21 ($CH_2Cl_2$)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.14 (s, 4H), 3.65 (t, *J* = 6.6 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.38 (s, 3H), 2.32 (s, 1H), 1.78 – 1.56 (m, 4H), 1.52 – 1.35 (m, 2H)

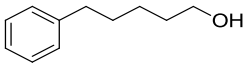
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 139.5, 135.0, 129.0, 128.3, 62.7, 35.5, 32.6, 31.5, 25.5, 21.0

**IR:** $\nu_{max}$ (film) 3332, 3018, 2929, 2857, 1515, 1457, 1048, 804 $cm^{-1}$

**MS:** *m/z* 178 [M]

**HRMS** calcd. for $C_{12}H_{18}O$ $[M-H_2O+H]^+$ *m/z* 161.1325 found 161.1326

### *5-phenylpentan-1-ol*



***R*$_f$** = 0.21 ($CH_2Cl_2$)

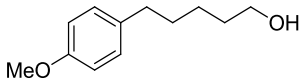
**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.37 – 6.95 (m, 5H), 3.51 (t, *J* = 6.6 Hz, 2H), 2.53 (t, *J* = 7.7 Hz, 2H), 1.90 (s, 1H), 1.70 – 1.40 (m, 4H), 1.40 – 1.18 (m, 2H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 142.6, 128.5, 128.3, 125.7, 62.8, 36.0, 32.6, 31.3, 25.5

**IR:** $\nu_{max}$ (film) 3333, 3026, 2931, 2857, 1603, 1585, 1495, 1453, 1050, 744, 696 $cm^{-1}$

**MS**: *m/z* 164 [M]

### *5-(p-methoxyphenyl)pentan-1-ol*




***R*$_f$** = 0.29 (EtOAc/heptane 1:2)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.10 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 3.62 (t, *J* = 6.5 Hz, 2H), 2.56 (t, *J* = 6.5 Hz, 2H), 1.69 (s, 1H), 1.60 (m, 4H), 1.40 (m, 2H)

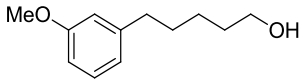
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 157.7, 134.8, 129.3, 113.8, 62.9, 55.3, 35.0, 32.7, 31.6, 25.4

**IR:** $\nu_{max}$ (film) 3337, 2931, 2856, 1612, 1510, 1462, 1299, 1242, 1176, 1034, 810 $cm^{-1}$

**MS:** *m/z* 194 [M]

**HRMS** calcd. for $C_{12}H_{18}O_2$ $[M-H_2O+H]^+$ *m/z* 177.1279 found 177.1273

### *5-(m-methoxyphenyl)pentan-1-ol*




***R*$_f$** = 0.29 (EtOAc/heptanes 1:2)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.20 (dd, *J* = 8.9, 7.6 Hz, 1H), 6.83 – 6.69 (m, 3H), 3.80 (s, 3H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.61 (t, *J* = 7.7 Hz, 2H), 1.76 – 1.54 (m, 5H), 1.47 – 1.33 (m, 2H).

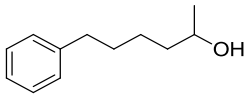
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 159.7, 144.4, 129.3, 121.0, 114.3, 111.0, 63.0, 55.3, 36.1, 32.8, 31.3, 25.5

**IR:** $\nu_{max}$ (film) 3337, 2932, 2857, 1601, 1584, 1487, 1453, 1436, 1257, 1151, 1042, 776, 694 $cm^{-1}$

**MS:** *m/z* 194 [M]

NMR data are in accordance with literature values.[127]

***6-phenylhexan-2-ol***



***R*$_f$** = 0.23 (EtOAc/heptane 1:4)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.32 – 7.15 (m, 5H), 3.79 (hex, *J* = 6.2 Hz, 1H), 2.63 (t, *J* = 7.7 Hz, 2H), 1.69 – 1.31 (m, 7H), 1.18 (d, J = 6.2 Hz, 3H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 142.7, 128.5, 128.4, 125.8, 68.2, 39.3, 36.0, 31.6, 25.6, 23.6

**IR:** $\nu_{max}$ (film) 3346, 3062, 3026, 2930, 2857, 1603, 1495, 1453, 1373, 1155, 1127, 1092, 1064, 930, 744, 697 $cm^{-1}$

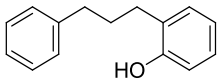
**MS:** *m/z* 178 [M]

**HRMS** calcd. for $C_{12}H_{18}O$ $[M-H_2O+H]^+$ *m/z* 161.1325 found 161.1323

### 3.4.4 General procedure for the ring-opening reaction of cyclic ethers with benzylmagnesium bromide

Benzylmagnesium bromide (2.5 mL, 0.66 M in tetrahydropyran, 1.65 mmol) was mixed with 3,3-dimethyloxetane (0.50 mL, 4.85 mmol) in a microwave vial under an argon atmosphere, and the vial was sealed. The reaction mixture was heated by microwave irradiation at the 180 °C for 4 hours. The mixture was cooled to ambient temperature, diluted with diethyl ether and the reaction was quenched with $H_2O$. The organic phase was washed with saturated aqueous $NH_4Cl$ and $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated. Column chromatography (1:6 EtOAc/heptane) produced 2,2-dimethyl-4-phenylbutan-1-ol (203 mg, 1.14 mmol, 69%).

### *2-(3-phenylpropyl)phenol*




***R*$_f$** = 0.25 (EtOAc/heptane 1:5)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.36 – 6.90 (m, 7H), 6.79 (td, *J* = 7.4, 1.2 Hz, 1H), 6.66 (dd, *J* = 7.9, 1.0 Hz, 1H), 4.54 (s, 1H), 2.74 – 2.46 (m, 4H), 2.01 – 1.75 (m, 2H)

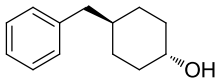
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 153.5, 142.4, 130.3, 128.6, 128.5, 128.2, 127.3, 125.9, 121.0, 115.4, 35.7, 31.3, 29.6

**IR:** $\nu_{max}$ (film) 3530, 3061, 3026, 2932, 2858, 1591, 1495, 1453, 1328, 1235, 1170, 1096, 1043, 747, 697 $cm^{-1}$

**MS:** *m/z* 212 [M]

**HRMS** calcd. for $C_{15}H_{16}O$ $[M+H]^+$ *m/z* 213.1274 found 213.1274

### *trans-4-benzylcyclohexan-1-ol*




***R*$_f$** = 0.29 (EtOAc/heptane 1:2)

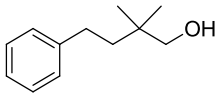
**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.46 – 7.00 (m, 6H), 3.55 (ddd, J = 10.7, 7.5, 3.3 Hz, 1H), 2.48 (dd, J = 7.1, 2.0 Hz, 2H), 2.04 – 1.83 (m, 2H), 1.72 (d, J = 12.1 Hz, 2H), 1.59 – 1.36 (m, 2H), 1.34 – 1.11 (m, 2H), 1.11 – 0.85 (m, 2H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 141.2, 129.2, 128.3, 125.9, 71.2, 43.4, 38.9, 35.6, 31.1'

**IR:** $\nu_{max}$ (film) 3259, 2924, 2852, 1450, 1369, 1083, 1043, 744, 697 $cm^{-1}$

**MS**: *m/z* 190 [M]

### *2,2-dimethyl-4-phenylbutan-1-ol*



***R*$_f$** = 0.33 (EtOAc/heptane 1:4)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.42 – 7.07 (m, 5H), 3.38 (s, 2H), 2.71 – 2.44 (m, 2H), 1.67 – 1.52 (m, 2H), 1.50 (s, 1H), 0.97 (s, 6H)

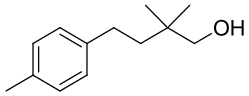
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 143.3, 128.5, 128.4, 125.8, 71.9, 41.0, 35.4, 30.6, 23.9

**IR:** $\nu_{max}$ (film) 3579, 3062, 3026, 2652, 2867, 1603, 1496, 1472, 1454, 1388, 1364, 1047, 1031, 762, 736, 697 cm$^{-1}$

**MS:** *m/z* 178 [M]

**HRMS** calcd. for $C_{12}H_{18}O$ $[M-H_2O+H]^+$ *m/z* 161.1325 found 161.1324

### *2,2-dimethyl-4-(p-tolyl)butan-1-ol*



***R*$_f$** = 0.29 (EtOAc/heptane 1:5)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.11 (s, 4H), 3.38 (d, *J* = 4.8 Hz, 2H), 2.65 – 2.47 (m, 2H), 2.33 (s, 3H), 1.72 – 1.43 (m, 3H), 0.97 (s, 6H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 140.2, 135.2, 129.2, 128.3, 71.9, 41.2, 35.4, 30.1, 23.9, 21.1

**IR:** $\nu_{max}$ (film) 3354, 3004, 2952, 2867, 1514, 1471, 1364, 1046, 1021, 808 cm$^{-1}$

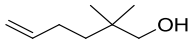
**MS**: *m/z* 192 [M]

**HRMS** calcd. for $C_{13}H_{20}O$ $[M-H_2O+H]^+$ *m/z* 175.1487 found 175.1481

### 3.4.5 General procedure for the ring-opening reaction of cyclic ethers with allylic magnesium chlorides

Allylmagnesium bromide (2.0 mL, 2.3 M in THF, 4.6 mmol) was mixed with 3,3-dimethyloxetane (0.50 mL, 4.85 mmol) in a microwave vial under an argon atmosphere, and the vial was sealed. The reaction mixture was heated by microwave irradiation at 120 °C for 30 minutes. The mixture was cooled to ambient temperature, diluted with diethyl ether and the reaction was quenched with $H_2O$. The organic phase was washed with saturated aqueous $NH_4Cl$ and $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated. Gradient column chromatography (1:1 -> 1:0 $Et_2O$/pentane) yielded 2,2-dimethylhex-5-en-1-ol (494 mg, 3.86 mmol, 84%).

#### *2,2-dimethylhex-5-en-1-ol*




***R*$_f$** = 0.32 ($Et_2O$/pentane 1:5)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 5.81 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 1H), 5.00 (ddd, *J* = 17.1, 3.5, 1.6 Hz, 1H), 4.95 – 4.88 (m, 1H), 3.30 (s, 2H), 2.15 – 1.92 (m, 2H), 1.69 (s, 1H), 1.42 – 1.21 (m, 2H), 0.87 (s, 6H)

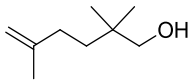
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 139.6, 114.1, 71.9, 37.9, 35.2, 28.5, 23.9

**IR:** $\nu_{max}$ (film) 3348, 3074, 2955, 2934, 2870, 1641, 1473, 1364, 1037, 992, 906 cm$^{-1}$

**MS**: *m/z* 128 [M]

**HRMS** calcd. for $C_8H_{16}O$ $[M+H]^+$ *m/z* 129.1274 found 129.1273

#### *2,2,5-trimethylhex-5-en-1-ol*




***R*$_f$** = 0.31 ($Et_2O$/pentane 1:5)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 4.82 – 4.56 (m, 2H), 3.32 (s, 2H), 2.05 – 1.88 (m, 2H), 1.73 (s, 3H), 1.50 (s, 1H), 1.47 – 1.27 (m, 2H), 0.88 (s, 6H)

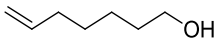
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 146.8, 109.5, 72.0, 36.8, 35.1, 32.2, 23.9, 22.8

**IR:** $\nu_{max}$ (film) 3355, 3074, 2938, 2917, 2870, 1649, 1472, 1448, 1051, 1033, 883 cm$^{-1}$

**MS:** *m/z* 142 [M]

**HRMS** calcd. for $C_9H_{18}O$ $[M+H]^+$ *m/z* 143.1430 found 143.1431

### *hept-6-en-1-ol*



***R*$_f$** = 0.41 ($Et_2O$/pentane 1:2)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.10 – 4.79 (m, 2H), 3.75 – 3.47 (m, 2H), 2.26 – 1.92 (m, 2H), 1.70 – 1.22 (m, 7H)

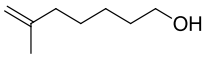
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 139.0, 114.5, 63.1, 33.8, 32.7, 28.8, 25.4

**IR:** $\nu_{max}$ (film) 3331, 3077, 2929, 2858, 1641, 1458, 1053, 993, 908 $cm^{-1}$

**MS:** *m/z* 115 [$MH^+$]

**HRMS** calcd. for $C_7H_{14}O$ $[M+H]^+$ *m/z* 115.1117 found 115.1123

### *6-methyl-hept-6-en-1-ol*



***R*$_f$** = 0.30 ($Et_2O$/pentane 1:1)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 4.83 – 4.52 (m, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.02 (t, *J* = 7.3 Hz, 2H), 1.80 – 1.25 (m, 9H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 146.1, 109.9, 63.1, 54.6, 37.9, 32.8, 27.4, 25.5, 22.5

**IR:** $\nu_{max}$ (film) 3331, 3074, 2932, 2859, 1649, 1449, 1374, 1052, 884 $cm^{-1}$

**MS:** *m/z* 128 [M]

**HRMS** calcd. for $C_8H_{16}O$ $[M+H]^+$ *m/z* 129.1274 found 129.1278

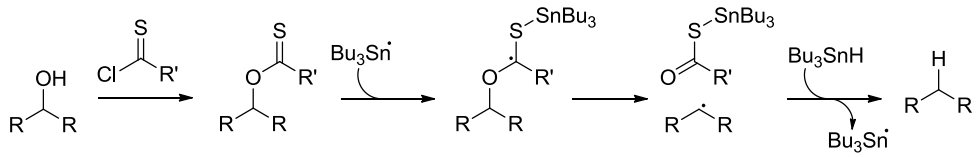
# Chapter 4: Iridium catalyzed dehydrogenative decarbonylation of primary alcohols in carbohydrates

In recent years, the catalysis research in the group of Prof. Robert Madsen has been focusing on transition metal-catalyzed reactions with alcohols. Within this portfolio, Olsen and Madsen have developed the iridium catalyzed dehydrogenative decarbonylation of primary alcohols forming one carbon shorter products and releasing molecular hydrogen and carbon monoxide.[128] Chapter 4 and Chapter 5 focus on two applications of the developed system.

## 4.1 Background

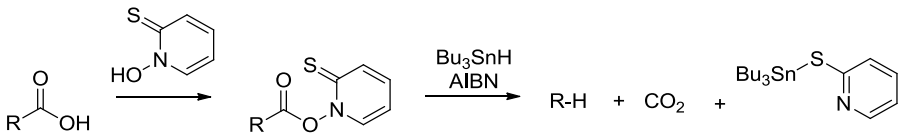
### 4.1.1 Traditional alcohol removal methods

One of the most important methods for deoxygenating secondary alcohols is the Barton-McCombie reaction.[129] The alcohol is first converted into the corresponding thiocarbonyl derivative and the subsequent treatment with $Bu_3Sn\cdot$ then results in the deoxygenated product (Scheme 33). The first tin radical is usually generated by AIBN from $Bu_3SnH$.




**Scheme 33 - Barton-McCombie reaction**

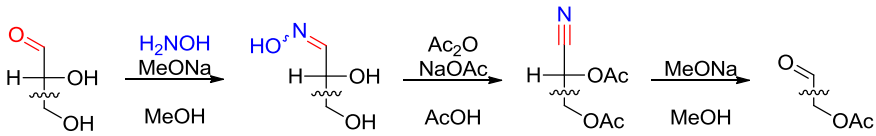
As the Barton McCombie reaction is designed for secondary alcohols and only the hydroxyl group is being removed in the reaction sequence, the result is not the same as in the dehydrogenative decarbonylation reaction described v*ide infra*. The same result is achievable by the Barton decarboxylation pathway (Scheme 34). First, the alcohol is oxidized into the carboxylic acid. Subsequently, the carboxylic acid is converted into a thiohydroxamate ester (Barton ester) which decarboxylates upon treatment with the tin radical.




**Scheme 34 - Barton decarboxylation.**

### 4.1.2 More classical carbohydrate carbon chain shortening procedures

The Barton decarboxylation is one example of a carbon shortening procedure that can be employed on carbohydrates. In the Wohl degradation - discovered over a century ago - 3 steps are required.[130–132] Initially the oxime is formed from the aldose and then in the following acetylation, the nitrile is formed from the oxime (Scheme 35). The subsequent treatment with sodium methoxide furnishes the one carbon shorter aldose.



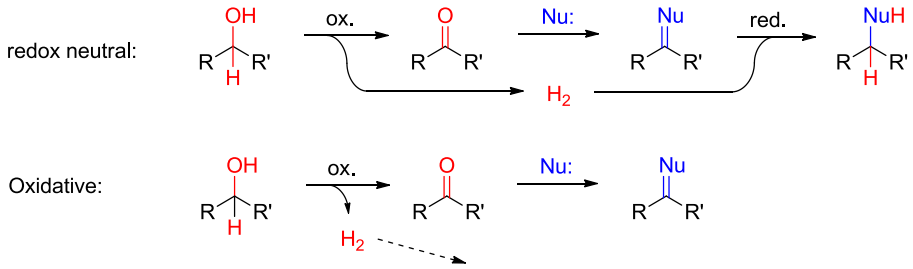

**Scheme 35 - Wohl degradation**

In the Ruff oxidative degradation, the aldonic acid salt is treated with $H_2O_2$ in the presence of iron(III) or copper(II) salts and the one carbon shorter aldose is formed.[133] Other procedures have been reported where aldoses are converted into their corresponding one carbon shorter aldonic acid salts.[134,135] All these methods require a stoichiometric amount of an activator or a reagent and they are therefore not very atom economically efficient.

### 4.1.3 Dehydrogenation of alcohols

It is well known that the carbon atom in an alcohol is much less electrophilic than in the corresponding tosylate or aldehyde. In the aspects of green chemistry, it is better to use the alcohol than the tosylate as the atom economy is better and less waste is being produced. By dehydrogenating the alcohol into an aldehyde, functionalization by a nucleophile becomes possible and multiple reviews address this strategy (Scheme 36).[136–139] This way can be referred to as “hydrogen borrowing

methodology”[136] as in the last step, hydrogenation (using the developed hydrogen from the dehydrogenation) of the unsaturated compound occurs. This is a redox neutral alcohol activation.




**Scheme 36 - Dehydrogenation and functionalization of alcohols.**

Some examples of nucleophiles employed are depicted in Figure 20. Wittig-type processes react with the *in situ* generated aldehyde.[140–142]

Aldol reactions with the aldehyde and either a ketone or an *in situ* generated ketone by ruthenium catalysis from a secondary alcohol also form C-C bonds.[143–145] Furthermore, the self condensation analogue is also referred to the Guerbet reaction and has been known for more than a century.[146,147]

Ruthenium catalysis can provide esters and lactones from primary and secondary alcohols in a redox neutral transformation.[148–151] In the Madsen group, self-coupling of primary alcohols into esters and a Guerbet type reaction from secondary alcohols by ruthenium catalysis have been reported under relatively mild conditions.[152] Under basic conditions a ruthenium pincer complex can also be used to prepare esters from alcohols, though under neutral condition the acetal could be formed instead.[153]

The first *N*-alkylation by homogeneous catalysis have been reported by the Griggs group where amines are produced from simple amines and oxidation of alcohols.[154] Amides can also be prepared from alcohols and amines by the liberation of $H_2$[155–157] and imines are similarly prepared by ruthenium catalysis with liberation of $H_2$ and $H_2O$.[158,159] Homogeneous catalysis also provides access to the aldehydes and ketones produced by dehydrogenation of an alcohol without further functionalization.[160–162]

Amines can also be dehydrogenated and functionalized although this will not be further described here.

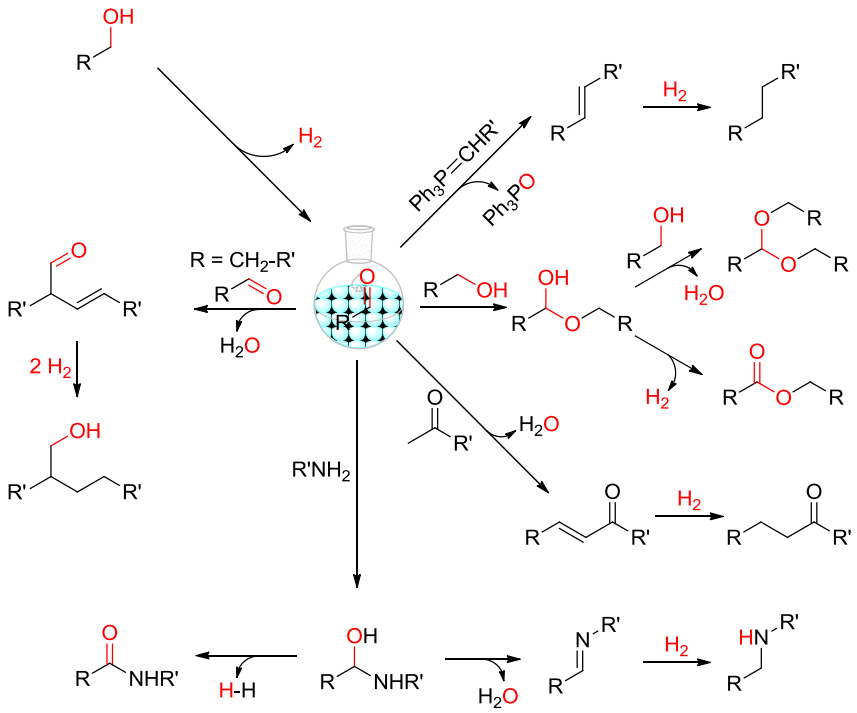
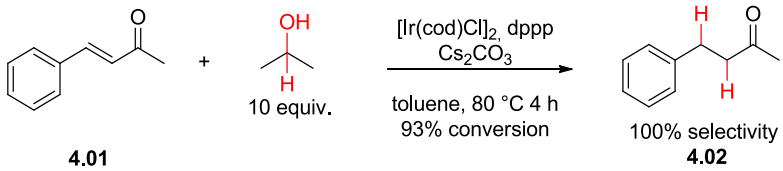



**Figure 20 - Overview of some possible functionalization of aldehydes**

The dehydrogenation of alcohols can also be used for other substrates, for example within the area of transfer hydrogenation. Often when reducing α,β-unsaturated ketones with traditional reducing agents, the ketone group is reduced chemoselectively and the olefin remains intact. For instance the reduction of benzylideneacetone (**4.01**) with DIBALH only provides the allyl alcohol,[163] but treatment of benzylideneacetone (**4.01**) with 10 equivalents of isopropanol under iridium catalysis provides 4-phenylbutan-2-one (**4.02**) with 100% selectivity (Scheme 37).[164] Thus, this result by Ishii and coworkers provides a convenient method of chemoselective hydrogenation of the C-C double bond in α,β-unsaturated ketones.




**Scheme 37 - Chemoselective hydrogenation of benzylideneacetone**

In addition to the chemoselective hydrogenations, enantioselective hydrogenation by homogeneous catalysis is also possible. Some of the most promising catalysts have been developed by Noyori and consist of a ruthenium metal with two coordination sites occupied by phosphine ligands and two sites with a diamine ligand.[165] Furthermore, some ruthenium complexes are able to racemize an enantiomerically pure secondary alcohol even at room temperature with only 0.5 mol% catalyst.[166,167] This has been exploited to perform dynamic kinetic resolution by the aid of an enzyme on secondary alcohols (Figure 21) and the outcome is an enantiomerically pure acetylated alcohol from a racemic mixture.

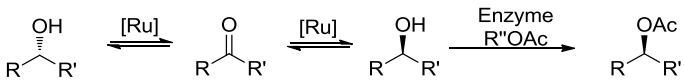
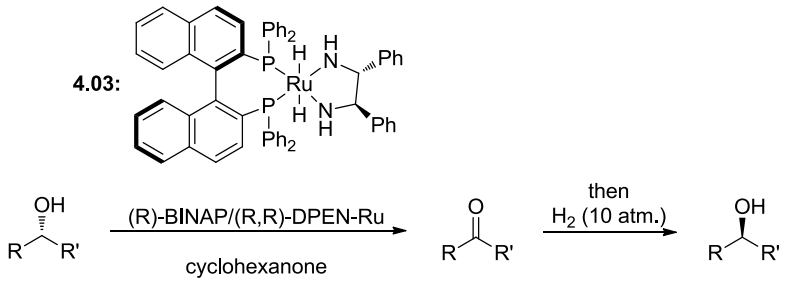



**Figure 21 – Dynamic kinetic resolution of secondary alcohols**

Adair and Williams reported a two-stage procedure for obtaining enantiomerically pure secondary alcohols from racemic secondary alcohols (Scheme 38).[168] First, the alcohol is oxidized by transfer hydrogenation with cyclohexanone using a Noyori hydrogenation catalyst **4.03**.[165] When the oxidation is completed the following hydrogenation occurs enantioselectively thereby regenerating the alcohol. In the Nishibayashi group the similar deracemization of secondary alcohols is performed by using two different ruthenium complexes for the oxidation and the subsequent reduction step.[169]




**Scheme 38 - Deracemization using Noyori catalyst.**

It is apparent that the most commonly applied transition metals for the dehydrogenation of alcohols are ruthenium and iridium although other metals are also being applied.

### 4.1.4 Mechanism for the dehydrogenation of alcohols

The hydrogen borrowing method relies on three steps: Dehydrogenation of the alcohol, functionalization of the aldehyde and hydrogenation. The functionalization step is often a traditional organic reaction and they are not much different mechanistically. More interesting are the mechanism for the dehydrogenation and the hydrogenation step. As the hydrogenation is thought to be the reverse reaction of the dehydrogenation, they are discussed simultaneously.

Two major pathways have been proposed for the hydrogen transfer to carbonyl groups.[170] In general "direct hydrogen transfer" is the primary pathway for main group metal catalyzed hydrogenations and a hydridic route is found for the transition metal catalyzed reactions. The first pathway is proposed for the Meerwein-Ponndorf-Verley reduction and the reverse Oppenauer oxidation (Figure 22). The same conditions – traditionally aluminum promoted - can be used for both of the reactions except that excess isopropanol is used for the reduction and excess acetone is used for the oxidation. The pathway is proposed to involve a 6-membered transition state with no hydride intermediates.

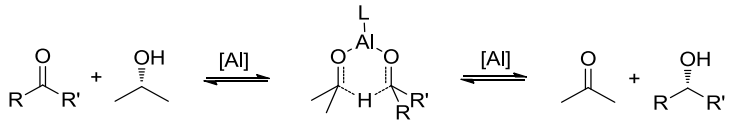



**Figure 22 – Meerwin-Ponndorf-Verley reduction and Oppenauer oxidation**

The hydridic route can be divided into a monohydride and a dihydride route and the route is dependent on the catalyst complex used. In the dihydride mechanism the two hydrogen atoms lose their identity and become equal after being transferred from the hydrogen donor to the metal complex. As an example, $Ru(PPh_3)_3Cl_2$ follows this mechanism.[171] In the monohydride mechanism the hydrogen atoms maintain their identity. This mechanism is followed by the Shvo's catalyst, a ruthenium complex. These two mechanisms can be distinguished experimentally by racemizing an optically active α-deuterated alcohol - a setup developed in the Bäckvall group (Figure 23).[171,172] In the dihydride pathway, scrambling of deuterium and hydrogen would occur if substrate **4.04** is racemized and in the monohydride pathway, no scrambling would occur.

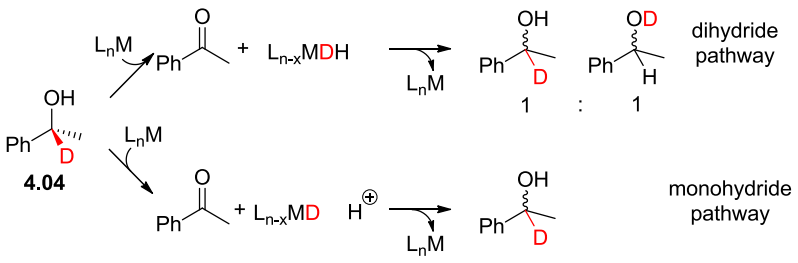



**Figure 23 - Bäckvall's setup for determining hydride mechanism**

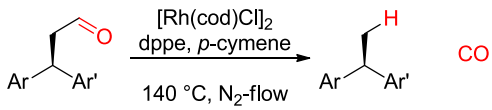
### 4.1.5 Decarbonylation of aldehydes

Decarbonylation of the *in situ* formed aldehyde has been a complicating factor in the "hydrogen borrowing method" strategies.[173,174] The decarbonylation has long been known to occur from aldehydes or acyl halides using either metallic palladium, Pd/C or rhodium.[175–181] Recently, Modak *et al.* have found that a catalytic amount of $Pd(OAc)_2$ without phosphine ligand decarbonylates aldehydes in the presence of air at 100-140 °C in a closed system.[182] Tsuji and Ohno have found that the neutral

Wilkinson catalyst ($RhCl(PPh_3)_3$, **4.05**) promotes the transformation stoichiometrically at room temperature or refluxing benzene and the reaction forms a very stable rhodium carbonyl complex, $Rh(CO)Cl(PPh_3)_2$ (**4.06**), that does not even revert back to complex **4.05** at 260 °C with excess triphenylphosphine added (Scheme 39).[177,178] On the other hand, it has been found that complex **4.06** is able to catalyze the decarbonylation reaction at 200 °C.[178]


**Scheme 39 - Decarbonylation by rhodium promotion**

The use of the bidentate ligands dppe and dppp instead of the two triphenylphosphine ligands is shown to have a higher catalytic activity.[183] The reaction with the cationic $[Rh(dppe)_2]Cl$ did not provide any isolatable carbonyl complex $[Rh(CO)(dppe)_2]$ and $[Rh(dppp)_2]Cl$ only have left behind a small amount of $Rh(CO)(dppp)_2$ when the reaction is quenched.[184] The cationic iridium catalyst with bidentate ligands show lower activity than their rhodium counterpart while the neutral complex $Ir(CO)Cl(PPh_3)_2$ (Vaska's complex) outperforms $Rh(CO)Cl(PPh_3)_2$ (**4.06**) and the cationic iridium systems.[185] The catalytic system with $[RhCl(cod)]_2$ and dppp also converts optically active β,β-diarylpropionaldehydes at around 140 °C into the corresponding 1,1-diarylethanes without losing the optical activity (Scheme 40).[186] This reaction is performed with a nitrogen flow to purge the CO, but the reaction can also be performed catalytically in a sealed tube if trifluoroethanol is used as the solvent.




**Scheme 40 - Decarbonylation of optically active β,β-diarylpropionaldehydes**

The mechanism have been investigated both theoretically and experimentally by the Madsen group.[187] All available data indicated that the starting point for the active catalytic cycle is the cationic $[Rh(CO)_2(dppp)]^+$ and the mechanism consisted of

oxidative addition, migratory extrusion and reductive elimination with the migratory extrusion as the rate-determining step (Figure 24).

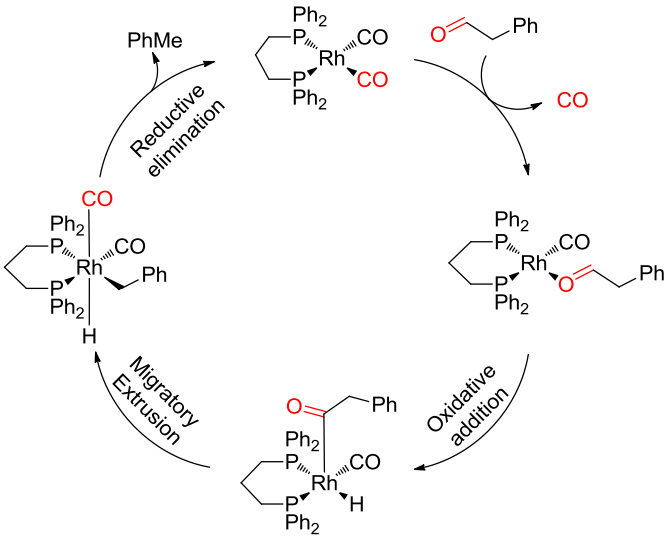
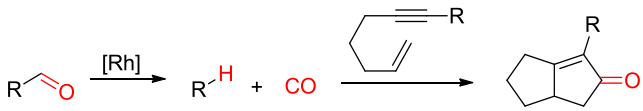



**Figure 24 - Mechanism for the rhodium catalyzed decarbonylation.**

The rhodium dimer complex $[Rh(PMe_3)_2Cl]_2$ is reported to decarbonylate aldehydes at about 100 °C and even though the reaction is not catalytic in a sealed vessel, purging the solution with an argon flow makes the transformation catalytic.[188] The cationic rhodium complex with a tridentate ligand, $[Rh(CO)(triphos)]^+$ is also capable of decarbonylating aldehydes in refluxing dioxane although the transformation is slow.[189] The catalytic decarbonylation of aldehydes could be performed at a temperature as low as room temperature using Wilkinson's catalyst (**4.05**) although this required a stoichiometric amount of a CO scavenger. In this manner diphenylphosphoryl azide $P(O)(OPh)_2N_3$ is transformed into $P(O)(OPh)_2(NCO)$.[190,191]

Coupling the rhodium catalyzed decarbonylation with a reaction that installs the carbonyl group is a way of using an aldehyde as a replacement for CO. In the Pauson-Khand reaction, an enyne is converted into bicyclic cyclopentenones with the aid of aldehydes (Scheme 41).[192]




**Scheme 41 - Using aldehydes as replacement for CO**

The removal of an aldehyde can be beneficial. If the aldehyde is needed for introducing other groups but is not needed in the final product then the removal of the group is necessary. For instance, α,β-unsaturated aldehydes have been used as alkene equivalents in the Diels-Alder reaction.[193] By performing the cycloaddition with butadiene and then executing the dehydrogenation reaction, cyclohexenes with no electron-withdrawing substituent can be obtained. Furthermore, chromones are easily accessable by performing an oxa-Michael addition of salicylaldehydes and α,β-unsaturated aldehydes and a subsequent decarbonylation.[194]

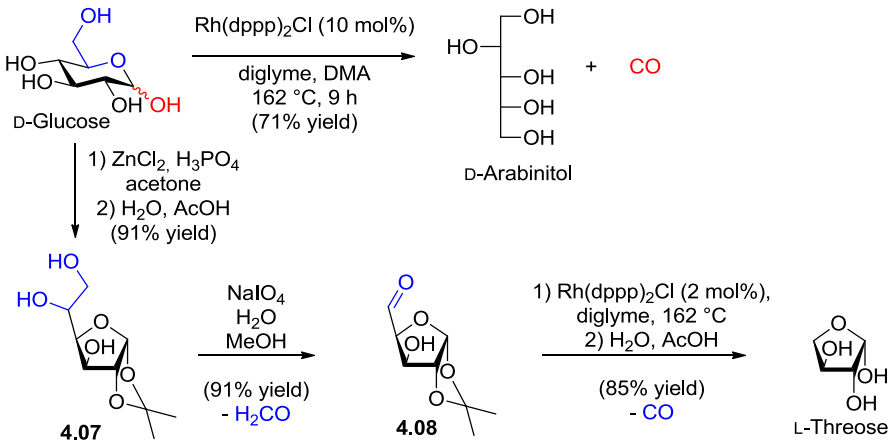
The description until now mainly focuses on rhodium and palladium as the transition metal for decarbonylation. Ruthenium is also able to decarbonylate an aldehyde, but the release of CO from the ruthenium complex is cumbersome and requires a CO abstractor to be catalytic. For instance it have been coupled with the Pauson-Khand type reaction.[195] Also light and a porphyrin can be employed to assist the release of CO.[196,197]

In contrast, iridium is found to be an excellent catalyst for the decarbonylation. Treating 2-naphthaldehyde with $[Ir(cod)Cl]_2$ and $PPh_3$ or $P(nBu)_3$ ligands in refluxing dioxane produces naphthalene in 95% yield after 24 hours.[198] Furthermore, hydroxymethylfurfural is selectively converted into furfuryl alcohol and a high pressure of $CO_2$ are used to dissolve and stabilize the hydroxymethylfurfural.[199]

### 4.1.6 Decarbonylation of carbohydrate aldoses

Wilkinsons catalyst (**4.05**) have been used for decarbonylating protected carbohydrate aldehydes.[200,201] Furthermore, decarbonylation of carbohydrates removes the anomeric carbon into the one carbon shorter alditols by treatment with a stoichiometric amount of Wilkinsons catalyst.[202] Later optimization by the Madsen group have found $Rh(dppp)_2Cl$ to be an efficient decarbonylation catalyst of

unprotected aldoses in refluxing diglyme.[203] Furthermore a route to L-threose from the most abundant carbohydrate source, D-glucose, by a strategy including a decarbonylation of an aldehyde have been achieved in an overall yield of 71% over 5 steps. In this route 2 carbons are removed: The first carbon is extruded by a sodium periodate cleavage of the diol in **4.07** and the second by decarbonylation of the aldehyde **4.08**. L-Threose is not available from natural sources and thereby this route provides easy access to an important chiral building block.



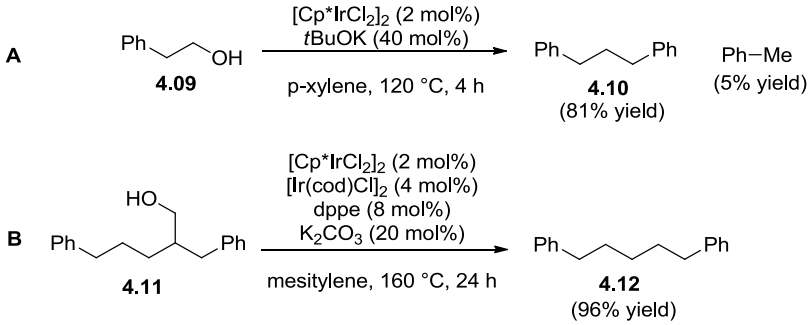

**Scheme 42 - Rhodium catalyzed decarbonylation of carbohydrates**

Ikeda *et al.* have utilized the aldoses as the source of carbon monoxide in the Pauson-Khand reaction. The installed carbonyl group originates from the anomeric position of the acetylated reducing sugar as confirmed by an experiment using a $^{13}C$ labeled carbon in the anomeric position.[204]

### 4.1.7 Dehydrogenative decarbonylation of primary alcohols

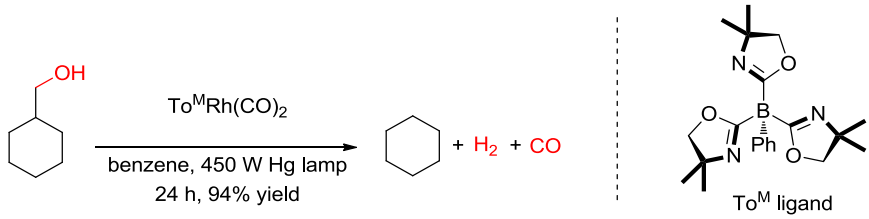
Ruthenium complexes have for a long time been known to stoichiometrically "decarbonylate" alcohols like ethanol under mild conditions.[205–208] The phrase, "decarbonylation of alcohols" covers the same as using the phrase "dehydrogenative decarbonylation of alcohols". In the past few years, a couple of examples exist where an alcohol is transformed into the one-carbon shorter dehydroxymethylated product. In the first example by Obora *et al.* α,ω-diarylalkanes are prepared from

ω-arylalkanols involving a Guerbet reaction.[209] The reaction is dependent on the substrates used. In the optimized conditions, 2-phenylethanol (**4.09**) is conveniently converted into 1,3-diphenylpropane (**4.10**) in 81% where only 5% of toluene is obtained. However, by employing the same conditions to 3-phenylpropanol only 14% of 1,5-diphenylpentane (**4.12**) is produced after 24 hours. The main product is the intermediate product **4.11**. As a consequence Obora *et al.* made a two step route to obtain the α,ω-diarylalkanes from ω-arylalkanols longer than two aliphatic carbons. The first step is under the same conditions as before. The second step under similar conditions as the dehydrogenative decarbonylation reaction described *vide infra*. They suggest that the last step proceeds in the following order: dehydrogenation, oxidative addition, decarbonylation, β-hydride elimination and hydrogenation.




**Scheme 43 - Formation of α,ω-diarylalkanes**

In a second example by Ho *et al.* the dehydrogenative decarbonylation is performed by using $To^{M}Rh(CO)_2$ at room temperature where the CO liberation is facilitated by photolysis under a 450 W medium pressure Hg lamp.[210] In the optimized conditions cyclohexylmethanol is converted into cyclohexane after 24 hours (Scheme 44). Besides aliphatic alcohols, the reaction also works on benzylic alcohols and of the few functional groups tested, the aryl fluoride, the methyl aryl ether and aliphatic silyl ether groups are stable. On the other hand, the methylaryl ester, the nitro aryl and the chloroaryl groups are not tolerated.

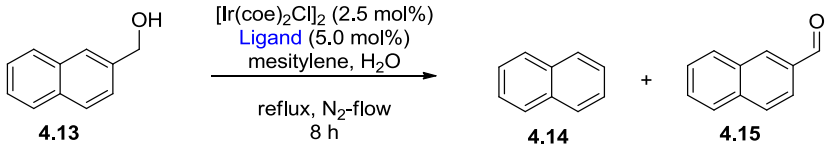



**Scheme 44 – Dehydrogenative decarbonylation using $To^{M}Rh(CO)_2$ and light**

As mentioned *vide supra*, $Pd(OAc)_2$ without phosphine ligands have been reported to decarbonylate aldehydes. An even more recent discovery by Modak *et al.* found that somewhat the same conditions also decarbonylate alcohols.[211] The yields of the decarbonylated products are decent to good and some substrates suffer from deoxygenated sideproduct formation. The oxidation of the primary alcohol into the corresponding aldehyde is proposed to be coupled with the reduction of $Pd(OAc)_2$ into Pd(0) while acetic acid is liberated. $O_2$ and the developed acetic acid then oxidizes Pd(0) back to $Pd(OAc)_2$ and $H_2O$ is formed.

The conditions for the iridium catalyzed dehydrogenative decarbonylation reaction have also been optimized by Olsen and Madsen.[128] An initial brief complex screening found $[Ir(coe)_2Cl]_2$ with either $PPh_3$ or BINAP to be the most promising iridium catalyst precursor. A ligand screening have been performed and some of the interesting results are listed in Table 15. Even though the monodentate ligands (ex. $PPh_3$) bound to iridium are excellent at the decarbonylation of aldehydes they work poorly in the dehydrogenative decarbonylation of alcohols (Table 15, entry 1-2). When a 1:1 ratio between iridium and $PPh_3$ is applied, a significant amount of 2-methylnaphthalene is produced. The bidentate ligands BINAP and BIPHEP with a bite angle of around 93° results in the highest yield of the investigated ligands (Table 15, entry 3-4).

**Table 15 – Dehydrogenative decarbonylation of (2-naphthyl)methanol**




| Entry | Ligand | Yield **4.14**[a] | Yield **4.15**[a] |
|---|---|---|---|
| 1 | $PPh_3$ | 17% | 34% |
| 2 | $PPh_3$[b] | 6%[c] | 44%[c] |
| 3 | BIPHEP | 59% | 27% |
| 4 | *rac*-BINAP | 61% | 20% |
| 5 | dppe | 9% | 42% |
| 6 | 3,3'-dpp-H8-[2,2']binaphthalene | 27% | 35% |

a) Determined by GC. b) 10.0 mol% $PPh_3$. c) 2-methylnaphthalene also formed in 41%.

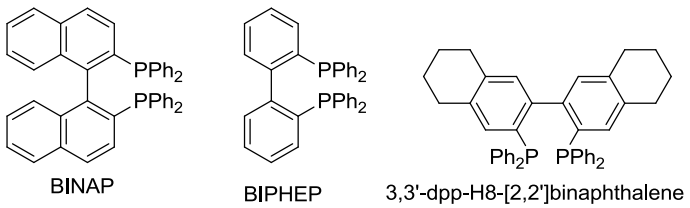



**Figure 25 - Ligands**

All these reactions are performed in mesitylene while other solvents resulted in a lower conversion rate. For instance, the reaction performed using diglyme as solvent gives 24% of naphthalene after 8 hours. $[Ir(coe)_2Cl]_2$ and $[Ir(cod)Cl]_2$ work equally well as the iridium source. The chloride ion is found to be the most optimal and addition of LiCl as well as using mesitylene saturated with $H_2O$ accelerated the reaction. The substrate scope of benzylic and aliphatic alcohols have been established and the ether-, tosyl-, chloro-, bromo-, ester-, thioether-, silyl ether- and phthalimido-functional groups are all tolerated. In general, the substrates are fully converted within 16 hours, although in the case of converting 2-hydroxymethyl-1,4-benzodioxane the reaction rate is slower. The cause of this will be discussed in section 4.2.5.

### 4.1.8 Mechanism for the dehydrogenative decarbonylation

The mechanistic details for the dehydrogenative decarbonylation have been explored by Olsen and Madsen.[212] These details can be useful for further optimization of the system and applications. Furthermore, deciphering the results produced in chapter 4 and chapter 5 of this thesis become more valid. A brief summary is given here.

By following the dehydrogenative decarbonylation transformation of (2-naphthyl)methanol (**4.13**) over time (2.5 mol% $[Ir(coe)_2Cl]_2$ and 5.0 mol% rac-BINAP), accumulation of 2-naphthaldehyde is observed. Furthermore, the catalyst is able to decarbonylate 2-naphthaldehyde (**4.15**). Therefore, it is evident that the overall transformation occurs with two distinct reactions. The relative rates of the two reactions are substrate dependent as accumulation of aliphatic aldehydes is rarely observed. By monitoring the gas development, ca. 1.8 mmol of gas is generated with the same reaction conditions from 1.0 mmol of (2-naphthyl)methanol (**4.13**), indicating that about 2 molecules of gas originate from the substrate. The first of the two gaseous molecules liberated is suggested to be $H_2$, originating from the dehydrogenation of the alcohol into the aldehyde. Diphenylacetylene, introduced in the reaction setup, is reduced to a mixture of stilbene and bibenzyl from hydrogenation using the developed $H_2$. The second gaseous molecule is suggested to be CO, originating from decarbonylation of the *in situ* generated aldehyde. In a two chamber setup, Vaska's complex is formed from $[Ir(cod)Cl]_2$, $PPh_3$ and the developed CO. The generation of $CO_2$ is excluded experimentally. When bobbling the generated gas flow through an aqueous solution of $Ca(OH)_2$, the existence of $CO_2$ would have generated $CaCO_3$ and this is not observed.

The proposed catalytic cycles are based on a more comprehensive study and all the arguments will not be stated in this thesis. The mechanism is divided into two distinct cycles (Figure 26). The left cycle is the dehydrogenation cycle which is initiated with a substitution with the alcohol on the starting complex **4.16**. Complex **4.17** is formed together with HCl which reversibly makes an oxidative addition to **4.16** and forms complex **4.21**. Complex **4.17** is neatly aligned for a β-hydride elimination in which **4.18**

is formed. Dissociation of the aldehyde left a vacant site in **4.19** for oxidative addition of HCl forming complex **4.20**. Reductive elimination ends the first cycle while $H_2$ is liberated.

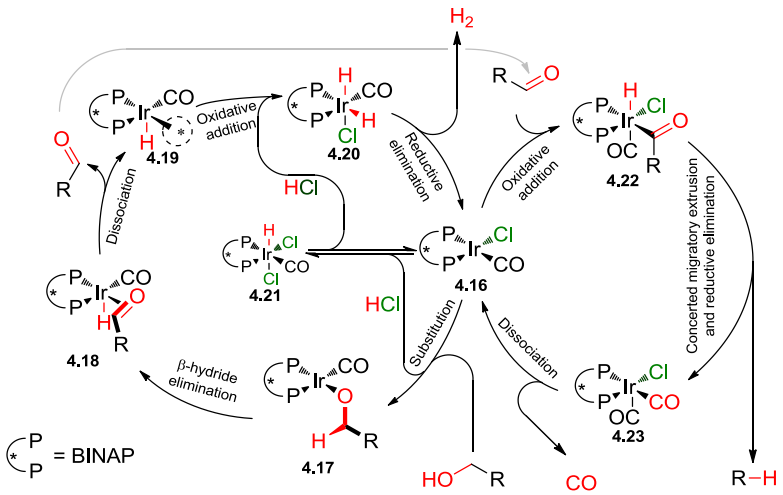
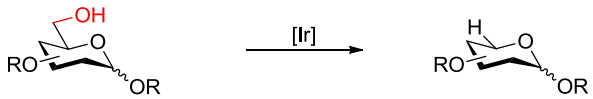



**Figure 26 - Proposed mechanism for the dehydrogenative decarbonylation reaction**

The right cycle is the decarbonylation cycle and begins with an oxidative addition of the developed aldehyde forming complex **4.22** from **4.16**. The following step is still not completely elucidated although they are believed to proceed via a concerted migratory extrusion and reductive elimination forming complex **4.23**. The overall transformation ends with a dissociation of the CO returning **4.16**. The CO dissociation is thought to be the rate determining step of the transformation and is most likely the reason for the fairly high temperatures needed in the reaction.

### 4.1.9 Project idea

The dehydrogenative decarbonylation reaction is shown to be an efficient transformation with simple aliphatic and benzylic primary alcohols. The possibility of using the reaction on more complicated substrates, such as carbohydrates, will expand the scope of the reaction (Scheme 45). The alcohols besides the primary alcohols need to be protected to avoid epimerization and to increase the solubility in the organic solvent. Optimization of the reaction is needed as more bulk is present in these substrates.

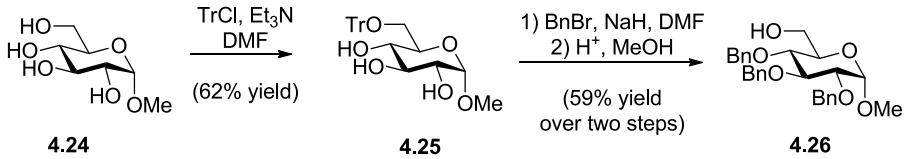



**Scheme 45 - Dehydrogenative decarbonylation of carbohydrates**

## 4.2 Results and discussion

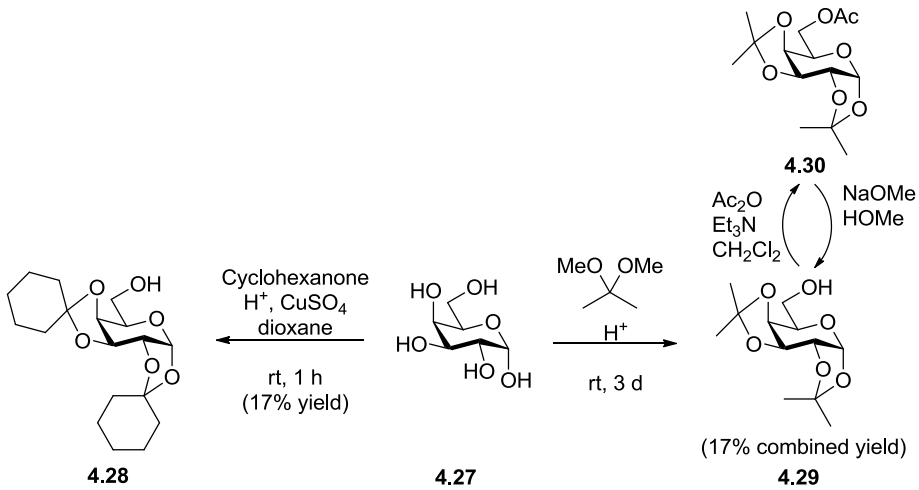
### 4.2.1 Substrate formation

Three carbohydrate substrates were prepared, which all contain an unprotected primary alcohol. Initially, methyl α-D-glucopyranoside (**4.24**) was selectively tritylated on the primary alcohol forming triol **4.25** in an isolated yield of 62% (Scheme 46). Triol **4.25** was benzylated on all the three available alcohol groups and the trityl group was cleaved under acidic conditions leaving monool **4.26** in 59% yield over two steps.




**Scheme 46 - Preparation of tribenzylated substrate 4.26**

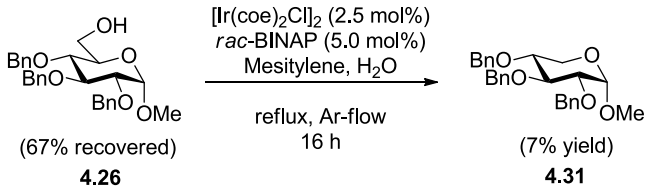
Treating D-galactose (**4.27**) with cyclohexanone under acidic condition placed the cyclohexylidene ketals in the 1,2 and 3,4 positions producing compound **4.28** (Scheme 47). The yield, however, was quite low. In a similar fashion the isopropylidene ketals were installed from D-galactose forming monol **4.29**. A copolar impurity was present which hampered the further transformations with this substrate. As monool **4.29** was not fully purified after column chromatography or distillation, it was acetylated into compound **4.30**. The purification of this compound was easier. Deacetylation reformed monool **4.29** as a pure compound.




**Scheme 47 - Preparation of dicyclohexylidene and diisopropylidene protected D-galactose**

### 4.2.2 Dehydrogenative decarbonylation of tribenzylated substrate 4.26

Previously, methyl 2,3,4-*O*-tribenzyl-D-xylopyranoside (**4.31)** have been synthesized as an alpha-beta mixture.[213] By applying the catalytic system developed by Olsen and Madsen on monool **4.26**, glycoside **4.31** could potentially be produced in a more convenient fascion.[128] Unfortunately, this only produced the D-xylopyranoside **4.31** in a low yield of 7% after 16 hours (Scheme 48). Only 67% of **4.26** was recovered which indicated that either the substrate or the desired product decomposed under these conditions. No intermediate aldehyde was observed in this reaction.




**Scheme 48 - Dehydrogenative decarbonylation of 4.26**

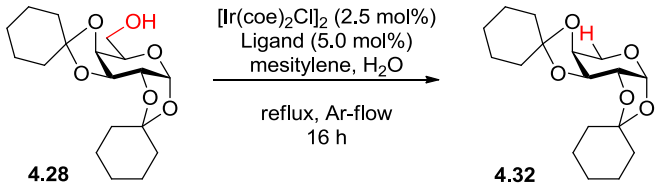
A reason for the low conversion rate can be the sterics originating from the benzyl group hindering the coordination of the active iridium catalyst. The reason for the decomposition may have been hydrogenolysis of some the benzyl ether groups by iridium catalysis. The required molecular hydrogen must have originated from the

dehydrogenation of the primary alcohol and the hydrogenolysis must have occured immediately thereafter as otherwise the hydrogen gas would have been liberated from the solution. Byproducts were not isolated and therefore it was not possible to determine whether cleavage of ether groups occurred. Another reason for the degradation could simply be the thermal instability of the substrate at the high temperatures required by the decarbonylation. Due to this instability this substrate was not used further.

### 4.2.3 Dehydrogenative decarbonylation of dicyclohexylidene substrate 4.28

Although L-arabinose is naturally available and the ketals are readily formed under acidic conditions, the transformation is still interesting synthetically.[214,215] Initially the cyclohexylidene protecting group was chosen because cyclohexanone has a higher boiling point than acetone. The compound might then be more stable towards decomposition if the conditions introduced the ketal/ketone in an equilibrium. A few experiments were performed with substrate **4.28** (Table 16).

**Table 16 - Dehydrogenative decarbonylation of dicyclohexylidene substrate 4.28**




| Entry | Ligand | Yield **4.28**[a] | Yield **4.32**[a] |
|---|---|---|---|
| 1[b] | - | 95% | - |
| 2 | *rac*-BINAP | 63% | 36% |
| 3 | dppe | 84% | 13% |

a) Isolated yield b) No iridium catalyst or ligand

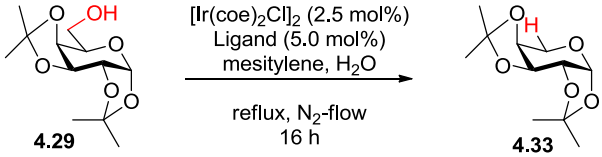
In the stability test with no catalyst, 95% of the substrate was recovered after a reaction time of 16 hours which was satisfying (Table 16, entry 1). Employing the iridium catalyst and the rac-BINAP ligand, 36% was converted into the desired L-arabinopyranoside product **4.32** after 16 hours (Table 16, entry 2). The conversion was still low and fortunately 63% of the monool **4.28** could be recovered. The dppe

ligand produced a lower conversion of 13% (Table 16, entry 2). The plan was to make a short ligand screening of the reaction with the monool **4.28** but then the focus switched to the monool **4.29**, containing the more commonly used isopropylidene protecting group.

### 4.2.3 Dehydrogenative decarbonylation of diisopropylidene substrate 4.29

A short ligand screening was performed on the diisopropylidine substrate **4.29**, and in general the compounds were also stable (Table 17). The same reaction time was used for easy comparison. The monodentate ligand was employed as a smaller ligand although this ligand gave a low conversion into of **4.33** (Table 17, Entry 1-2) as the previous results (Table 15, Entry 3-4, Page 95). BINAP and BIPHEP gives the best yield in the previous ligand screening and were also tried here. A racemic mixture and the *R*-configuration of BINAP resulted in a comparable yield around 30% of **4.33** (Table 17, Entry 3-4). No atropisomerisation of the BINAP ligand was expected to occur as the atropisomerization energy barrier was too high.[216] As BIPHEP is a smaller ligand than BINAP, it was expected to result in a higher yield but only 21% of **4.33** was obtained (Table 17, Entry 5). The more flexible ligand 3,3'-dpp-H8-[2,2']binaphthalene resulted in the highest yield of 40% of **4.33** (Table 17, Entry 6). The yield was increased further to 49% by the addition of LiCl to stabilize the active catalyst (Table 17, Entry 7). Naturally, twice the high catalyst loading also results in a higher yield of **4.33** (Table 17, Entry 8). Using tetraline as a solvent instead of mesitylene and thereby increasing the temperature did not increase the yield of the reaction (Table 17, Entry 9). The material also seemed to decompose as TLC-analysis showed additional spots and a lower yield of the starting material **4.29** was recovered.

**Table 17 - Dehydrogenative decarbonylation of diisopropylidene substrate 4.29**




| Entry | Ligand | Yield **4.29**[a] | Yield **4.33**[a] |
|---|---|---|---|
| 1 | $PPh_3$ | 93% | 3% |
| 2 | $PPh_3$[b] | 86% | 2% |
| 3 | *rac*-BINAP | 66%[c] | 29%[c] |
| 4 | *R*-BINAP | 58%[d] | 32%[d] |
| 5 | BIPHEP | 67% | 21% |
| 6 | 3,3'-dpp-H8-[2,2']binaphthalene | 58%[d] | 40%[d] |
| 7 | 3,3'-dpp-H8-[2,2']binaphthalene[e] | 38% | 49% |
| 8 | 3,3'-dpp-H8-[2,2']binaphthalene[f] | 39% | 60% |
| 9 | 3,3'-dpp-H8-[2,2']binaphthalene[g] | 64% | 7% |

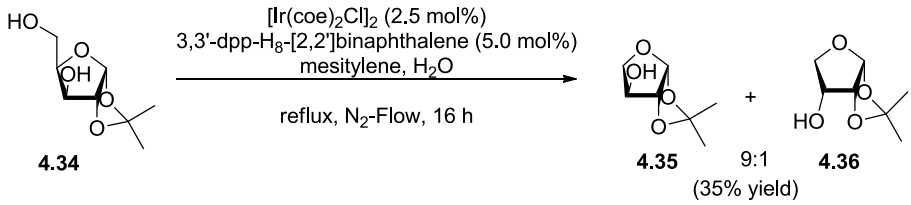
a) Isolated yield. b) 10.0 mol% $PPh_3$. c) Average over two runs. d) Average over 3 runs. e) 10 mol% LiCl added. f) 5.0 mol% $[Ir(coe)_2Cl]_2$ and 10.0 mol% 3,3'-dpp-H8-[2,2']binaphthalene. g) Tetraline used as solvent

In the mechanism of the dehydrogenative decarbonylation it was postulated that HCl was stored by the iridium complex **4.21** (Figure 26, Page 97). In the dehydrogenative decarbonylation of diisopropylidene monool **4.29,** deprotection of the isopropylidene groups were not observed even though this could occur under acidic conditions. This observation indicated that the complexation of HCl in the formation of complex **4.21** was extremely efficient and complex **4.21** was not deprotecting the isopropylidene groups.

### 4.2.4 Dehydrogenative decarbonylation of isopropylidene substrate 4.34

The yields were still not satisfying within the desired reaction time and it was thought that the steric demand from the substituent on C(4) is slowing the reaction down. Accordingly, a reaction on an even less hindered carbohydrate **4.34** was performed.

The isopropylidene group was stable in the previous case and therefore it was also employed in this substrate.

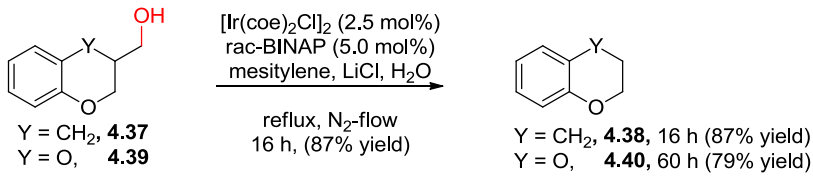



**Scheme 49 - Dehydrogenative decarbonylation of isopropylidene substrate 4.34**

The yield of the dehydrogenative decarbonylation products **4.35** and **4.36** from **4.34** after 16 hours was 35% (Scheme 49), a little bit lower than with the previous substrate **4.29**. According to TLC-analysis, all the substrate was consumed. The product ratio was 9:1 (analysed by $^{1}$H-NMR) in favor of the compound with retained stereochemical configuration at C(3) and therefore the iridium catalyst had scrambled the stereochemical configuration of the secondary alcohol positioned on C(3). More reactions with this substrate were not pursued.

### 4.2.5 Aftermath

After the reactions in chapter 4 were performed, the reaction with 3-hydroxymethyl-chromane (**4.37**) was carried out (Scheme 50).




**Scheme 50 – Dehydrogenative decarbonylation of 3-hydroxychromane**

This result and the lowered conversion rate of 3-hydroxymethyl-1,4-benzodioxane (**4.39**) also highlighted the plausible reason for the slow conversion rate of the carbohydrate substrates. The structure of 3-hydroxymethyl-1,4-benzodioxane (**4.39**) resembles the structure of most carbohydrates with non-protected primary alcohols (Figure 27).

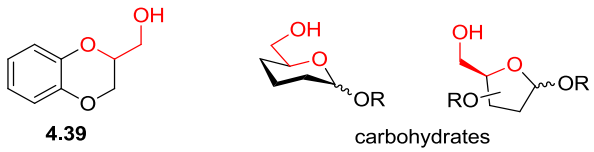



**Figure 27 - Comparison of chromane 4.37 and carbohydrates**

The conversion of 3-hydroxymethyl-chromane (**4.37**) was much faster than the conversion of benzodioxane **4.39**. Furthermore, following the benzodioxane **4.39** reaction over time, no aldehyde was accumulated. It was postulated that the endocyclic oxygen must be able to reversibly coordinate to iridium forming a less active catalyst (Figure 28). The site for β-hydride elimination was hindered and therefore the dehydrogenation cycle in the overall mechanism must be slower than with the simple substrates (Figure 26, Page 97).

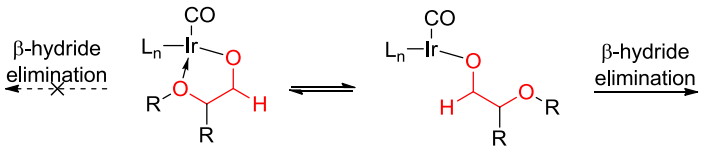



**Figure 28 - Proposed coordination by oxygen to the iridium atom**

## 4.3 Conclusion and further perspectives

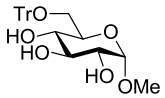
The dehydrogenative decarbonylation reaction has been successful for some of the investigated substrates. The reaction rate was slow but a good yield could be obtained by employing a longer reaction time. At this point, other projects got a higher priority. The project was not fully discarded though a novel ligand design may increase the rate of the reaction and therefore work in this project may resume at a later time.

## 4.4 Experimental

### 4.4.1 General methods

The same general methods as described in section 2.4.1 were followed. Furthermore, 1,2-*O*-isopropylidene-α-D-xylofuranose (**4.34**) was in stock from previous group members and used without further purification.[203] DMF was dried over 4Å molecular sieves. Methanol was dried over 3Å molecular sieves. $CuSO_4$ was dried in an oven at 185 °C.

### 4.4.2 Formation of methyl 6-*O*-trityl-α-D-glucopyranoside (4.25)



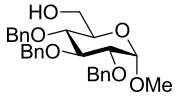

To methyl α-D-glucopyranoside (**4.24**) (2.415 g, 13.11 mmol) in dry DMF (20 mL) was added freshly distilled triethyl amine (1.9 mL, 13.71 mmol) and trityl chloride (3.782, 13.57 mmol). A condenser was attached and the reaction was heated at 90 °C for 4 hours. The mixture was concentrated, and the residue was dissolved in $CH_2Cl_2$. The organic phase was washed twice with $H_2O$, dried with $Na_2SO_4$, filtered and concentrated. Crystallization from toluene afforded methyl 6-*O*-trityl-α-D-glucopyranoside (**4.25**) (3.551 g, 8.135 mmol, 62%) as a white solid.

**$^1$H NMR:** $\delta_H$ (400 MHz, Acetone-$d_6$): 7.52 (d, *J* = 7.5 Hz, 6H), 7.39 – 7.24 (m, 9H), 4.73 (d, *J* = 3.7 Hz, 1H), 3.98 (s, 1H), 3.85 – 3.71 (m, 1H), 3.61 (t, *J* = 9.1 Hz, 1H), 3.48 (s, 3H), 3.46 – 3.35 (m, 2H), 3.35 – 3.17 (m, 2H), 2.85 (s, 1H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, Acetone-d6): 145.3, 129.6, 128.6, 127.8, 100.9, 87.0, 75.5, 73.5, 72.1, 72.0, 64.8, 55.2

NMR data are in accordance with literature values.[217]

### 4.4.3 Two-step procedure for the formation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (4.26)




To methyl 6-*O*-trityl-α-D-glucopyranoside (**4.25**) (3.498 g, 8.050 mmol) in dry DMF (15 mL) were added NaH (1.9 g, 55% oil suspension, 26 mmol), benzyl bromide (3.1 mL, 26 mmol) and TBAI (100 mg, 0.27 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for 20 hours. NaH (390 g, 55% oil suspension, 5.4 mmol) and benzyl bromide (0.60 mL, 5.0 mmol) were added and the reaction stirred for an additional hour. The mixture was diluted with $Et_2O$ and quenched with $H_2O$. The organic phase was separated and washed with brine and $H_2O$, dried with $Na_2SO_4$, filtered and concentrated.

The residue was dissolved in dry MeOH (15 mL) and a few drops of concentrated sulphuric acid were added. After 1 hour, the suspension was quenched by adding sodium carbonate. The mixture was stirred for 15 minutes and then concentrated. The residue was diluted with $CH_2Cl_2$ and washed with brine. The organic phase was dried with $MgSO_4$, filtered and concentrated. Gradient column chromatography (EtOAc/heptane 2:5->1:1) furnished methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**4.26**) (2.20 g, 4.74 mmol, 59%) as a white solid

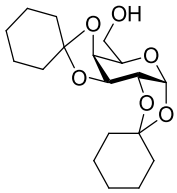
$\boldsymbol{R_f}$ = 0.2 (EtOAc/heptane 1:3)

**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 7.41 – 7.27 (m, 15H), 5.00 (d, *J* = 10.9 Hz, 1H), 4.89 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 10.9 Hz, 1H), 4.81 (d, *J* = 12.1 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 11.0 Hz, 1H), 4.57 (d, *J* = 3.5 Hz, 1H), 4.01 (t, *J* = 9.3 Hz, 1H), 3.83 – 3.61 (m, 3H), 3.57 – 3.47 (m, 2H), 3.37 (s, 3H), 1.63 (t, *J* = 6.3 Hz, 1H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 138.9, 138.3, 138.3, 128.6, 128.6, 128.6, 128.3, 128.2, 128.1, 128.1, 128.0, 127.8, 98.3, 82.1, 80.1, 77.5, 75.9, 75.2, 73.6, 70.8, 62.0, 55.3

NMR data are in accordance with literature values.[218]

### 4.4.4 Formation of 1,2;3,4-di-*O*-cyclohexylidene-α-D-galactopyranose (4.28)



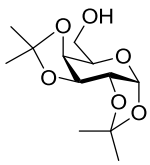
To D-galactose (21.436 g, 119.0 mmol) in dioxane (40 mL) was added cyclohexanone (40.0 mL, 386 mmol), anhydrous $CuSO_4$ (14.87 g, 93.2 mmol) and concentrated $H_2SO_4$ (4 mL). The suspension turns into a red slurry mass after 1 hour and was diluted with EtOAc followed by filtration of the mixture. The organic phase was washed with saturated aqueous $NaHCO_3$ and $H_2O$. The organic phase was dried with $Na_2SO_4$, filtered and concentrated. Dry column chromatography (EtOAc/heptane 1:20) produced 1,2;3,4-di-*O*-cyclohexylidene-α-D-galactopyranose (**4.28**) (9.537 g, 20.5 mmol, 17%).

$R_f$ = 0.39 (EtOAc/heptane 1:2)

**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 5.57 (d, *J* = 5.0 Hz, 1H), 4.63 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.35 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.27 (dd, *J* = 7.9, 1.5 Hz, 1H), 3.88 (p, *J* = 6.9 Hz, 2H), 3.75 (t, *J* = 6.8 Hz, 1H), 2.20 (s, 1H), 1.90 – 1.27 (m, 20H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 110.2, 109.4, 96.1, 71.5, 70.6, 70.3, 68.2, 62.7, 35.8, 35.7, 34.4, 34.0, 25.2, 25.1, 24.1, 24.0, 23.8, 23.7

### 4.4.5 Formation of 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (4.29)



D-Galactose (6.277 g, 34.8 mmol) was suspended in 2,2-dimethoxypropane (40 mL) followed by an addition of concentrated $H_2SO_4$ (3 drops). The suspension dissolves after 1½ days. After a total of 3 days, the mixture was neutralized by $NaHCO_3$ and concentrated. The residue was dissolved by $CH_2Cl_2$ and washed with brine. The organic phase was dried with $Na_2SO_4$, filtered and concentrated. Column

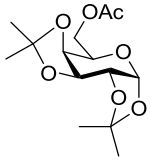
chromatography (EtOAc/heptane 1:4) produced 1,2;3,4-di-*O*-cyclohexylidene-α-D-galactopyranose (**4.29**) (0.750 g) and unpure fractions (1.981 g).

The unpure fractions (1.981 g) were dissolved in dry $CH_2Cl_2$ (4.0 mL) followed by addition of $Et_3N$ (1.20 mL, 8.61 mmol) and $Ac_2O$ (0.76 mL, 8.1 mmol). After 18 hours, the mixture was diluted with $CH_2Cl_2$ and washed with saturated aqueous $NaHCO_3$. The organic phase was dried with $Na_2SO_4$, filtered and concentrated. Column chromatography (EtOAc/heptane 1:3) produced 6-*O*-acetyl-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4.30**) (1.075 g).

The latter product (989 mg) was dissolved in methanol and NaOMe was added. After 15 minutes the mixture was concentrated. The residue was dissolved in $CH_2Cl_2$ and washed with $H_2O$. The organic phase was dried with $Na_2SO_4$, filtered and concentrated into 1,2;3,4-di-*O*-cyclohexylidene-α-D-galactopyranose (**4.29**) (0.773 g). The products were collected (1.523, 5.85 mmol, 17%).

$\boldsymbol{R_f}$ = 0.37 (EtOAc/heptane 1:1)
**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 5.56 (d, *J* = 5.0 Hz, 1H), 4.61 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.33 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.27 (d, *J* = 7.9 Hz, 1H), 3.92 – 3.82 (m, 2H), 3.81 – 3.70 (m, 1H), 2.18 (s, 1H), 1.53 (s, 3H), 1.45 (s, 3H), 1.33 (s, 6H)
**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 109.6, 108.8, 96.4, 71.8, 70.9, 70.7, 68.2, 62.5, 26.2, 26.1, 25.1, 24.4
NMR data are in accordance with literature values.[219]

### *6-O-Acetyl-1,2;3,4-di-O-isopropylidene-α-D-galactopyranose (4.30)*



***R*$_f$** = 0.30 (EtOAc/heptane 1:3)

**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 5.54 (d, *J* = 5.0 Hz, 1H), 4.62 (dd, *J* = 7.9, 2.5 Hz, 1H), 4.32 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.31 – 4.14 (m, 3H), 4.05 – 3.98 (m, 1H), 2.08 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H)

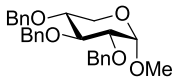
**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 171.1, 109.8, 108.9, 96.5, 71.2, 70.8, 70.6, 66.1, 63.6, 26.2, 26.1, 25.1, 24.6, 21.1

NMR data are in accordance with literature values.[220]

### 4.4.6 General procedure for the dehydrogenative decarbonylation reaction

Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**4.26**) (488 mg, 1.05 mmol), $[Ir(coe)_2Cl]_2$ (22.4 mg, 0.025 mmol) and rac-BINAP (32.0 mg, 0.051 mmol) were added to a Schlenk tube which was flushed with an argon. The mixture was dissolved in mesitylene (2.0 mL) and stirred at 170 °C for 16 hours with an argon flow. After allowing the mixture to reach room temperature, gradient column chromatography (EtOAc/heptane 1:4->1:2) afforded the product methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranoside (**4.31**) (34 mg, 0.078 mmol, 7%) and recovered methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**4.26**) (326 mg, 0.702 mmol, 67%).

### *Methyl 2,3,4-tri-O-benzyl-α-D-xylopyranoside (4.31)*

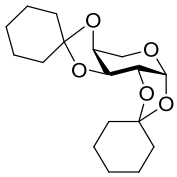


**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.58 – 7.15 (m, 15H), 4.94 (d, *J* = 10.9 Hz, 1H), 4.88 (d, *J* = 10.9 Hz, 1H), 4.85 – 4.58 (m, 4H), 4.53 (d, *J* = 3.6 Hz, 1H), 3.98 – 3.86 (m, 1H), 3.67 – 3.42 (m, 4H), 3.38 (s, 3H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 139.0, 138.3, 128.5, 128.5, 128.2, 128.2, 128.0, 127.9, 127.7, 98.4, 81.6, 79.7, 78.2, 76.0, 73.6, 60.0, 55.3

$^1$H NMR data are in accordance with literature values.[213]

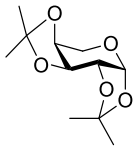
### *1,2;3,4-Di-O-cyclohexylidene-β-L-arabinopyranose (4.32)*



**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 5.49 (d, *J* = 5.0 Hz, 1H), 4.56 (dd, *J* = 7.8, 2.3 Hz, 1H), 4.30 (dd, *J* = 5.0, 2.3 Hz, 1H), 4.25 – 4.16 (m, 1H), 3.82 (dd, *J* = 12.9, 2.1 Hz, 1H), 3.65 (dd, *J* = 12.9, 1.2 Hz, 1H), 2.07 – 1.11 (m, 23H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 109.5, 109.1, 95.6, 70.5, 70.3, 69.6, 60.4, 35.8, 35.8, 34.4, 33.7, 25.3, 25.1, 24.1, 24.0, 23.8, 23.7

### *1,2;3,4-Di-O-isopropylidene-β-L-arabinopyranose (4.33)*



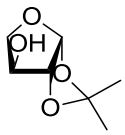
***R*$_f$** = 0.40 (EtOAc/heptane 1:3)

**$^{1}$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 5.50 (d, *J* = 5.0 Hz, 1H), 4.56 (dd, *J* = 7.9, 2.3 Hz, 1H), 4.30 (dd, *J* = 5.0, 2.3 Hz, 1H), 4.22 (d, *J* = 7.9 Hz, 1H), 3.83 (dd, *J* = 12.9, 1.9 Hz, 1H), 3.66 (d, *J* = 12.9 Hz, 1H), 1.53 (s, 3H), 1.48 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 109.1, 108.6, 96.0, 70.9, 70.7, 70.0, 60.3, 26.2, 26.2, 25.1, 24.4

$^{1}$H NMR data are in accordance with literature values.[221]

### *1,2-O-Isopropylidene-β-L-threofuranose (4.35)*



***R*$_f$** = 0.47 (EtOAc/heptane 2:1)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) *inter alia*: 5.94 (d, *J* = 3.7 Hz, 1H), 4.48 (d, *J* = 3.6 Hz, 1H), 4.25 (d, *J* = 2.6 Hz, 1H), 4.07 (dd, *J* = 10.1, 2.7 Hz, 1H), 3.86 (dd, *J* = 10.1, 1.0 Hz, 1H), 2.44 (s, 1H), 1.46 (s, 4H), 1.30 (s, 4H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$) *inter alia*: 111.9, 105.3, 85.1, 75.3, 73.0, 26.8, 26.3

NMR data are in accordance with literature values.[222]

# Chapter 5: Reductive carbonylation of aryl bromides with syngas liberated by the dehydrogenative decarbonylation of primary alcohols

## 5.1 Background

This chapter describes the work on coupling the dehydrogenative decarbonylation reaction with a reductive carbonylation reaction using a two chamber system. As most of the background theory covering the former transformation has been described in chapter 4, background about the latter reaction is described in this chapter.

### 5.1.1 Production of syngas

Synthesis gas (in short, syngas) is a fuel gas mixture primarily consisting of CO and $H_2$ and often also $CO_2$. The industrial production of syngas is via a gasification process where carbonaceous materials are heated with an oxidizing agent (also called gasifying agents).[223] The oxidant can be oxygen, steam, $CO_2$ or a mixture of these. The reactions involved in the gasification process using these oxidants are combustion, Boudouard reaction and steam gasification (Figure 29).

gasification: $C \xrightarrow{\frac{1}{2} O_2} CO$

combustion: $C \xrightarrow{O_2} CO_2$

Boudouard reaction: $C \xrightarrow{CO_2} 2\ CO$

steam gasification: $C \xrightarrow{H_2O} CO + H_2$

**Figure 29 - Gasification processes**

The gasification of coal can be achieved at 900 °C.[224] Due to the depletion of fossil fuels, the employment of biomass and solid wastes have been intensified in recent years. Raw syngas from coal, pet coke, petroleum residues etc. also contain small amounts of $CH_4$, $H_2S$, $N_2$, $NH_3$, HCN, Ar, COS, Ni and Fe besides the syngas mixture. Clean-up techniques exist for the purification of the syngas and are classified

according to the gas temperature exiting the cleanup device: hot (temperature above 300 °C), warm and cold (temperature under 100 °C) gas cleaning regimes.[225] Cold gas cleanup are highly effective although they often produce waste water streams and they might be energy inefficient. A major advantage of the hot gas cleanup is that they avoid cooling and reheating the gas stream. Milder conditions have recently been reported for the release of syngas from biomass and alcohols since the release could occur below 250 °C with the use of iridium, platinum or a tin-promoted Raney-nickel catalyst.[128,226,227]

### 5.1.2 Industrial applications of syngas

Syngas has plenty of industrial applications (Figure 30).[228] For fuel cells, a high content of $H_2$ can be obtained by adjustment via the water-gas shift reaction. In this reaction CO and $H_2O$ are converted into $H_2$ and $CO_2$.[229] The molecular hydrogen produced in the water-gas shift reaction can also be used for the production of ammonia by iron catalysis in the Haber-Bosch process.[230] Syngas can catalytically be transformed into a wide range of hydrocarbons, alcohols, aldehydes, ketones and acids. This process is known as the Fischer-Tropsch synthesis when the products are mainly liquid hydrocarbons. The production of methanol can be seen as a variant of the Fischer-Tropsch synthesis while carbon fuels are accessible *via* further purification following these processes. The process can be performed by a high-pressure method catalyzed with a zinc-chromium catalyst (commercialized by BASF in 1923) or a low-pressure method catalyzed by a copper-zinc-chromium catalyst (first introduced by ICI in 1966). Among many applications, methanol can be used as a fuel alone or blended with gasoline. Furthermore, it can be transformed into gasoline by the Mobil MTG (methanol to gasoline) process.

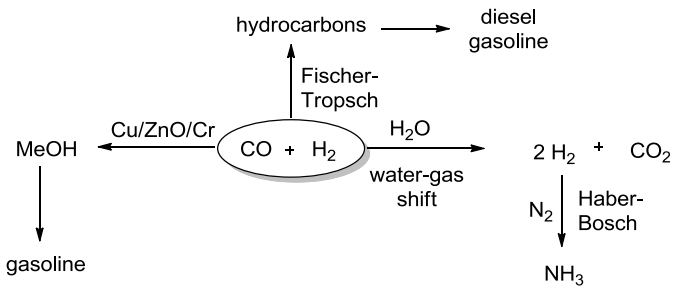
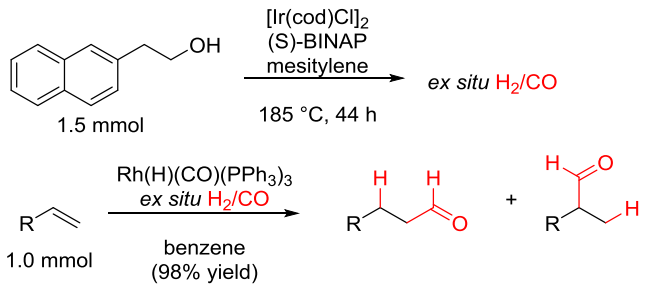



**Figure 30 - Industrial applications of syngas**

### 5.1.3 Applications of syngas in organic chemistry

#### *Hydroformylation*

The amount of available transformations using syngas in organic chemistry is still limited. One of the processes known is the hydroformylation.[231] It was discovered by Roelen in 1938 and has found important applications in industry. The reaction produces a one-carbon elongated product as a linear or branched aldehyde from an olefin. Recently, *ex situ* generated syngas from the iridium catalyzed dehydrogenative decarbonylation have been applied to perform the hydroformylation in a two-chamber setup by Andersson and coworkers.[232] Their optimal syngas source is 2-naphtylethanol in mesitylene with complete chemoselectivity (Scheme 51). They also found that D-sorbitol in diethyleneglycol diethyl ether work to some extent although it suffers in the selectivity as phenylethane is also produced in a significant amount.

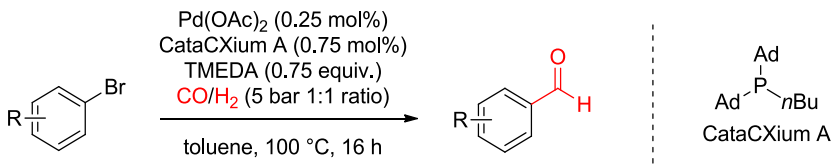



**Scheme 51 - Hydroformylation using *ex situ* syngas**

### *Reductive carbonylation*

Having a halide group on the aryl moiety serves as an excellent handle for attaching functional groups and has been employed for several carbonylation procedures.[233,234] Among these are the palladium catalyzed reductive carbonylation as discovered by Schoenberg and Heck in 1974.[235] In this reaction, an aryl or vinyl halide is converted into the corresponding aldehyde with the use of syngas. High pressures of CO were needed in specific high-pressure equipment as the typical reaction has been performed at 80-100 bars. To achieve the formylation at a low pressure of CO the use of an expensive reductive agent such as polymethylhydrosiloxane or triethyltin hydride have been necessary.[236,237] Furthermore, formate salts[238,239] have been used as the hydride source. Ueda *et al.* have recently reported a transformation of aryl bromides to aldehydes by using formylsaccharin as the CO source in the presence of triethyltin hydride.[240]

Within the last decade the Beller group has developed a low pressure system for the reductive carbonylation using syngas.[241–243] In the optimized system an aryl bromide is converted into the corresponding aldehyde using $Pd(OAc)_2$, CataCXium A ($P(1\text{-}Ad)_2nBu$), TMEDA, and 5 bar syngas in toluene at 100 °C (Scheme 52).




**Scheme 52 - Reductive carbonylation of aryl bromides**

They employ a ligand to Pd ratio of 3:1 to stabilize the palladium catalyst and to prevent the formation of palladium carbonyl clusters. The conversion rate naturally increases at higher temperature although this occurs at the expense of the chemoselectivity as the reductive dehalogenation becomes faster. The maximum yield is found at a total pressure around 5 bars.

A Hammett study shows that the rate of the reaction is enhanced by a decreased electron density of the aromatic ring. Therefore, it is likely that the oxidative addition

of the aryl bromide to palladium **5.01** is the rate limiting step (Figure 31). The Beller group later has reported a comprehensive study of the mechanism using CataCXium A, P($t$Bu)$_2$$n$Bu and P($t$Bu)$_3$ ligands and the results support this theory.[244] The resting states in the catalytic cycle has been implied to be $Pd_n(CO)_mL_n$ **5.06** and Pd(Br)(H)$L_2$ **5.07** and these complexes probably do not lie within the cycle. As the reaction proceeds, the concentration of the catalytically active species is low and therefore the oxidative addition of **5.01** to **5.02** becomes the rate limiting step. Furthermore **5.06** is thermally unstable and decomposes to give palladium black and free ligand. When excess ligand and TMEDA are employed, **5.07** is dominant and this species is stable at 100 °C under syngas.

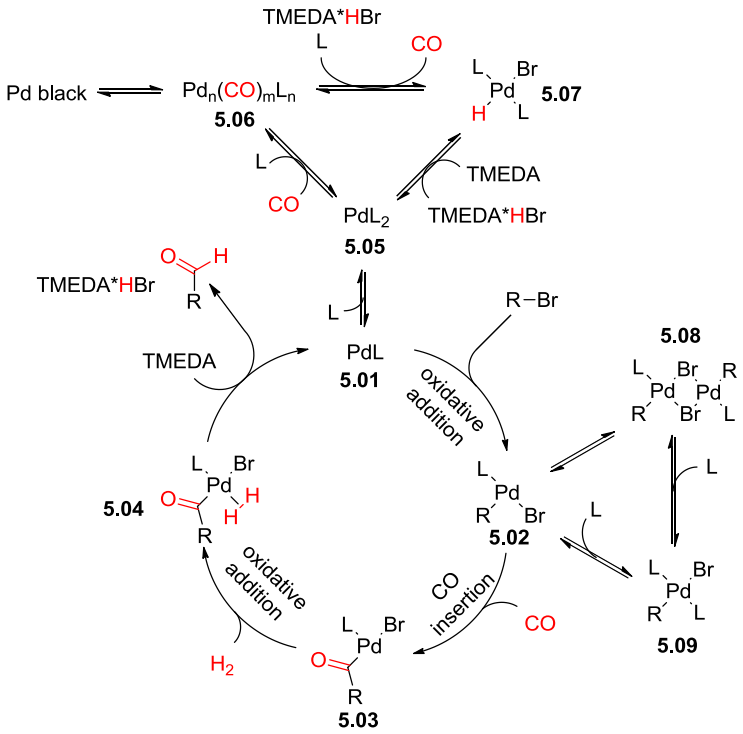
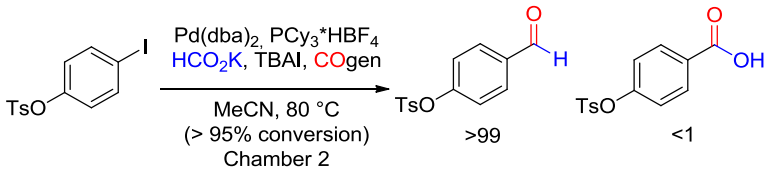



**Figure 31 - Proposed mechanism for the reductive carbonylation of aryl bromides**

After CO insertion of complex **5.02**, complex **5.03** is formed. When P(*t*Bu)$_3$ is applied as ligand, complex **5.03** is very stable and lowes the conversion rate of the reaction significantly. As CataCXium A and P(*t*Bu)$_2$*n*Bu have similar rates and are faster than P(*t*Bu)$_3$ the *n*Bu group seems to be very important in the ligand. Using these ligands, the complex **5.03** can be hydrogenolyzed presumably in a heterolytic cleavage with TMEDA via **5.04** and completing the cycle with the release of the aryl aldehyde and the TMEDA*HBr salt. Noteworthy, the complexes that contain more than one equivalent of ligand versus palladium are outside the catalytic circle. Theoretically, decreasing the P/Pd ratio from the ratio the Beller group has employed to a ratio of 1:1 would accelerate the conversion rate and hopefully still avoid the formation of palladium black. Garrou and Heck has previously shown that decreasing the concentration of phosphine ligand in the carbonylation of complexes like **5.02** had a lower rate for the formation of CO inserted complexes like **5.03**.[245]

The reaction also works well for aryl and vinyl bromides though higher pressures of CO and a ligand change to a novel ligand design are needed for the conversion of triflates.[246,247]

The Skrydstrup group has been performing reductive carbonylation on aryl iodides by using *ex situ* generated CO and potassium formate as the hydride source.[248] The CO is liberated from a palladium catalyzed reaction on COgen (9-methyl-9*H*-fluorene-9-carbonyl chloride) in a separate chamber of a two-chamber system. The optimal conditions for the reductive carbonylation is with PCy$_3$*HBF$_4$ as the ligand and provides >95% conversion and is >99:1 selective favoring the aldehyde over the carboxylic acid (Scheme 53). CataCXium A has performed almost as well although the aldehyde/acid selectivity was 98:2. Though they initially have employed a P/Pd ratio of 2:1, decreasing this increased the selectivity favoring the aldehyde. The functional group tolerance is good and examples of $^{13}$C and deuterium labeling have been demonstrated.




**Scheme 53 - Reductive carbonylation in two-chamber systems**

### 5.1.4 Project idea

The dehydrogenative decarbonylation reaction develops syngas in a $CO/H_2$ ratio of 1:1. The reductive carbonylation reaction consumes equimolar amounts of CO and $H_2$. The idea of this project is two combine these two reactions. By using a two-chamber system and by performing the syngas producing reaction in chamber one should provide the gasses needed in the syngas consuming reductive carbonylation reaction in chamber 2. Conditions for the reactions in both chambers will be tested. The potential aspect of employing a carbohydrate syngas source will also be explored.

## 5.2 Results and discussion

Experimental work in this project has been performed in collaboration with Ph.D. Esben Olsen, Bach. Polyt Samuel Elliot and *Cand.* Polyt Jascha Rosenbaum

### 5.2.1 Optimization of the syngas consuming chamber

As described in section 5.1.3, the conditions for the reductive carbonylation has been optimized by Beller's group[241,242] and by Skrydstrup's group.[248] The conditions were slightly different as the pressure was expected to be lower, and the initial production of gas by the dehydrogenative decarbonylation was not necessarily distributed evenly between CO and $H_2$. The Skrydstrup and Andersson groups have already been using a two chamber system. We needed to perform the reactions in the two chambers at different temperatures and therefore - to fit our needs - we designed new glassware in collaboration with the department glass blower, Patrick Scholer.

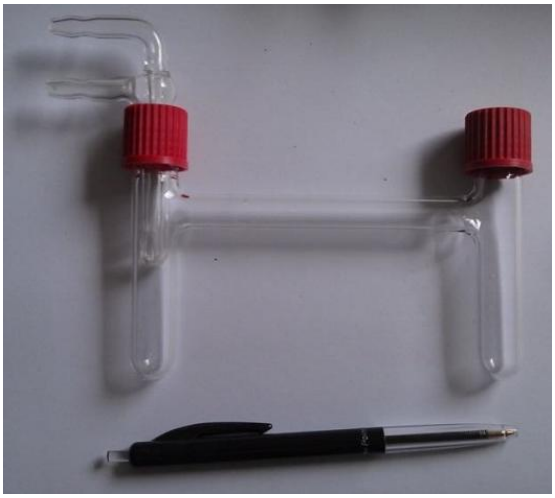
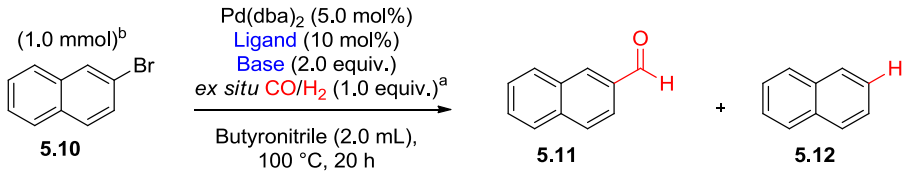


**Figure 32 - The two chamber system**

A short optimization of the reductive carbonylation was performed by *Cand.* Polyt Jascha Rosenbaum during his master studies.[249] 2-(2-Naphthyl)ethanol was chosen as the syngas source since the product has a boiling point below the reaction temperature. Also, accumulation of 2-(2-Naphthyl)ethanal was not observed with this substrate and the amount of syngas formed in the reaction can be calculated by GC-

analysis. A P/Pd ratio of 2:1 was applied and a very short extension of the base screening showed that TMEDA was more promising than $Cy_2NMe$ and $K_2CO_3$ (Table 18, Entry 1-3). TMEDA was also applied in the Beller system.[241,242] The short ligand screening showed that CataCXium A compared to the other ligands resulted in a higher conversion and selectivity favoring the aldehyde **5.11** (Table 18, Entry 3-6).

**Table 18 - Optimization of base and ligand in the reductive carbonylation using *ex situ* syngas in a two chamber system**

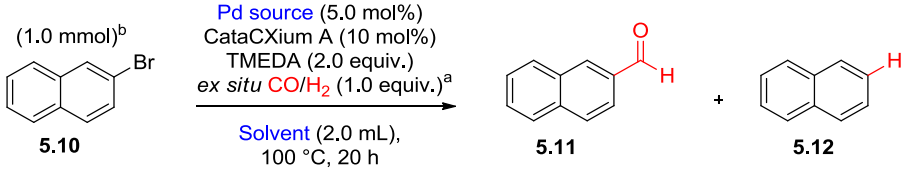



| Entry | Ligand | Base | gas formed[c] | Conv.[d] **5.10** | Yield[d] **5.11** | Yield[d] **5.12** |
|---|---|---|---|---|---|---|
| 1 | $PCy_3{\cdot}HBF_4$ | $Cy_2NMe$ | 32% | 15% | 7% | 8% |
| 2 | $PCy_3{\cdot}HBF_4$ | $K_2CO_3$ | 30% | 6% | 1% | 5% |
| 3 | $PCy_3{\cdot}HBF_4$ | TMEDA | 38% | 10% | 7% | 3% |
| 4 | $P(tBu)_3{\cdot}HBF_4$ | TMEDA | 26% | 2% | <1% | 2% |
| 5 | $PMe(tBu)_2{\cdot}HBF_4$ | TMEDA | 47% | 22% | 17% | 5% |
| 6 | CataCXium A | TMEDA | 57% | 38% | 27% | 11% |

a) Syngas formed in chamber 1: 2-(2-naphthyl)ethanol (1.0 mmol), $[Ir(cod)Cl]_2$ (2.5 mol%), *rac*-BINAP (5.0 mol%), LiCl (25 mol%) and mesitylene (2.0 mL, contains 150 ppm $H_2O$). b) Reductive carbonylation performed in chamber 2. c) Gas formed determined by GC chromatogram from chamber 1 of the conversion of 2-(2-naphthyl)ethanol using standard curves of the compounds. d) Conversion and yield determined by GC chromatogram from chamber 2 using standard curves of the compounds

Looking into different solvents, toluene and butyronitrile gave similar results (Table 19, Entry 1 and 3). The reaction in mesitylene at 125 °C resulted in a lower yield as the selectivity was poorer (Table 19, Entry 2). Toluene is a less expensive solvent than butyronitrile and was therefore used for further reactions. The conversion was increased to 51% by employing $Pd(OAc)_2$ as the Pd source with similar selectivity (Table 19, Entry 4) and $Pd(OAc)_2$ was therefore used further on.

**Table 19 - Optimization of solvent and Pd source in the reductive carbonylation using *ex situ* syngas in a two chamber system**




| Entry | Pd source | solvent | gas formed[c] | Conv.[d] **5.10** | Yield[d] **5.11** | Yield[d] **5.12** |
|---|---|---|---|---|---|---|
| 1[e] | $Pd(dba)_2$ | butyronitrile | 57% | 38% | 27% | 11% |
| 2[f] | $Pd(dba)_2$ | mesitylene | 49% | 34% | 15% | 19% |
| 3 | $Pd(dba)_2$ | toluene | 55% | 35% | 24% | 11% |
| 4 | $Pd(OAc)_2$ | toluene | 62% | 51% | 33% | 18% |

a) Syngas formed in chamber 1: 2-(2-naphthyl)ethanol (1.0 mmol), $[Ir(cod)Cl]_2$ (2.5 mol%), *rac*-BINAP (5.0 mol%), LiCl (25 mol%) and mesitylene (2.0 mL, contains 150 ppm $H_2O$). b) Reductive carbonylation performed in chamber 2. c) Gas formed determined by GC chromatogram from chamber 1 of the conversion of 2-(2-naphthyl)ethanol using standard curves of the compounds. d) Conversion and yields determined by GC chromatogram from chamber 2 using standard curves of the compounds. e) Same as (Table 18, Entry **6**). f) Performed at 125 °C

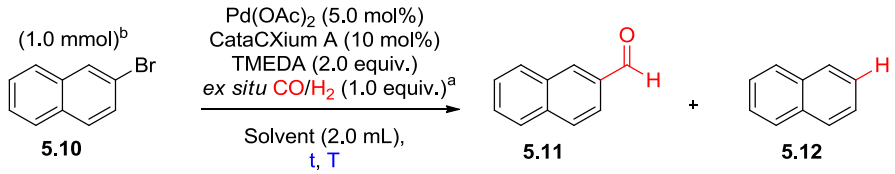
Using 3 equivalents of ligand versus Pd like in the Beller system did lower the conversion to some extent (Table 20, entry 2). In the Skrydstrup system, the equimolar amount of ligand versus Pd have been working well and later reactions in this thesis are also performed with only a slight excess of ligand versus Pd.

Andersson and coworkers added methyl benzoylformate in chamber one for capturing and storing molecular hydrogen, thereby increasing the initial concentration of CO versus $H_2$.[232] Adding 1.0 of mmol methyl benzoylformate to chamber 1 in our system dramatically lowered the conversion (Table 20, entry 3).

The reactions were performed at a lower pressure than in the 5 bars in Bellers system.[241,242] This may reduce the conversion rate of the reaction and this hypothesis was confirmed by increasing the reaction time from 20 to 44 hours. In this case, full conversion was achieved and the yield of the aldehyde **5.11** was increased to 43% (Table 20, entry 4). Lowering the temperature to 80 °C further increased the yield to

70% (Table 20, entry 5). Lowering the temperature to 65 °C lowered the conversion significantly (Table 20, entry 6). Therefore it was decided to perform the following reactions at 80 °C.

**Table 20 - Optimization of time and temperature in the reductive carbonylation using *ex situ* syngas in a two chamber system**



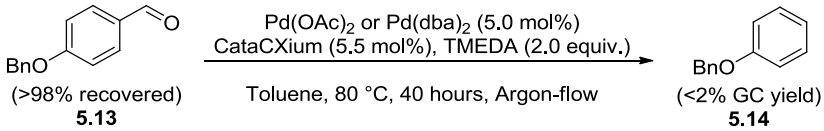

| Entry | t (°C) | T (h) | gas formed[c] | Conv.[d] **5.10** | Yield[d] **5.11** | Yield[d] **5.12** |
|---|---|---|---|---|---|---|
| 1[e] | 100 | 20 | 62% | 51% | 33% | 18% |
| 2[f] | 100 | 20 | 53% | 35% | 24% | 11% |
| 3[g] | 100 | 20 | 50% | 4% | 2% | 2% |
| 4 | 100 | 44 | 82% | >99% | 43% | 57% |
| 5 | 80 | 44 | >99% | >99% | 70% | 30% |
| 6 | 65 | 44 | 40% | 14% | 12% | 2% |

a) Syngas formed in chamber 1: 2-(2-naphthyl)ethanol (1.0 mmol), $[Ir(cod)Cl]_2$ (2.5 mol%), *rac*-BINAP (5.0 mol%), LiCl (25 mol%) and mesitylene (2.0 mL, contains 150 ppm $H_2O$). b) Reductive carbonylation performed in chamber 2. c) Gas formed determined by GC chromatogram from chamber 1 of the conversion of 2-(2-naphthyl)ethanol using standard curves of the compounds. d) Conversion and yields determined by GC chromatogram from chamber 2 using standard curves of the compounds. e) Same as (Table 18, Entry **6**). f) 15 mol% instead of 10 mol% CataCXium A was used. g) Methyl benzoylformate (1.0 mmol) was added to chamber 1.

An interesting observation was that the reaction in the gas producing chamber stalled if the reaction in gas consuming chamber was not progressing. We postulate that, when the pressure of CO in the two-chamber system was sufficiently high, the iridium dicarbonyl complex **4.23** in chamber one was not able to dissociate more CO from the complex and therefore the reaction stops.

As mentioned in section 4.1.5, it is well known that palladium under certain conditions are able to decarbonylate aldehydes. It was tested whether the product **5.12** originates from decarbonylation of **5.11**. The reaction was performed with only a

small excess of ligand versus Pd and with an argon flow to make the carbonylation more favorable. Only traces of **5.14** was observed after 40 hours of reaction time from 4-(benzyloxy)benzaldehyde (**5.13**) (Scheme 54). According to the optimization study of the palladium catalyzed decarbonylation performed by Modak *et al.,* the study confirms that the conditions we used for the reductive carbonylation also was expected to suppress the decarbonylation process.[182] They found that toluene is a less efficient solvent than cyclohexane or dichloroethane that have been used for the best conditions. Also the presence of a base and a phosphine ligand together with the absence of molecular sieves and air has been suppressing the decarbonylation reaction. The reduced product **5.12** was therefore believed to origin from the reductive dehalogenation of the bromide **5.11**.




**Scheme 54 – Decarbonylation test**

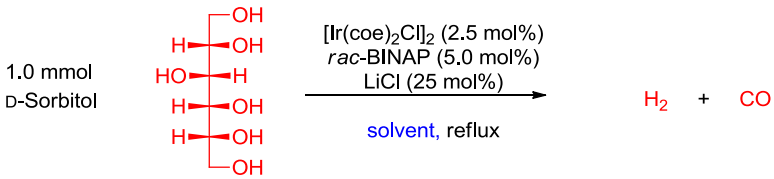
At this point no further optimization in the syngas consuming chamber was performed well-knowing that a reaction time of 44 hours is not ideal. The focus was switched towards finding the optimal syngas source.

### 5.2.2 Gas development from carbohydrates

In the ideal case the syngas source would be carbohydrates because they are abundant in nature and no waste products would be produced. Prior to optimizing the reductive carbonylation reaction, the gas evolution from the dehydrogenative decarbonylation of D-sorbitol was monitored in different solvents. If we assume the gas follows the ideal gas law, 1 mmol of gas equals a volume of 24.1 mL at room temperature. If one mmol of D-sorbitol was fully converted into syngas, 13 mmol of gas would be liberated. Selected curves are depicted in Figure 33 and the maximum amount of gas liberated from the reactions are listed in Table 21. The optimal conditions for aromatic and aliphatic alcohols with mesitylene did only produce 7.8 mL of gas (Table 21, Entry 1). Gradually increasing the amount of diglyme also

increased the amount of gas developed (Table 21, Entry 2-5). The reaction using diglyme as the only solvent produced the most gas as a little more than 1 mmol gas was developed. In the reactions above, a black precipitate was observed, which indicate that iridium was converted into an inactive species.

**Table 21 - Gas development, solvent screening**




| Entry | Solvent one (V/mL, $H_2O$/ppm[a]) | Solvent two (V/mL, $H_2O$/ppm[a]) | $V_{max}$ (mL)[b] | T (h)[c] |
|---|---|---|---|---|
| 1 | mesitylene (2.0, 150) | - | 7.8 | 2 h |
| 2 | mesitylene (1.5, 150) | diglyme (0.5, 1150) | 16.6 | 5 h |
| 3 | mesitylene (1.0, 150) | diglyme (1.0, 1150) | 16.0 | 3 h |
| 4 | mesitylene (0.5, 150) | diglyme (1.5, 1150) | 27.0 | 3.5 h |
| 5 | diglyme (2.0, 1150) | - | 25.6 | 3.5 h |
| 6 | diglyme (2.0, 200) | - | 29.2 | 5.5 h |
| 7 | DMA (2.0,-) | - | 8.8 | 40 min |
| 8 | BMICl[d] | - | 3.7 | 16 min |

a) $H_2O$ content measured by Karl Fischer instrument prior to reaction. b) Volume of gas where no further gas development is observed. c) Reaction time where $V_{max}$ is reached. d) 1.96 g BMICl (1-butyl-3-methylimidazolium chloride) used as an ionic liquid solvent

A control experiment with no D-sorbitol in the reaction showed that gas was developed by diglyme itself (Figure 33). The reaction was performed at 170 °C and therefore the diethers in diglyme were not stable and decomposed with gas evolution. Applying this to the two-chamber system converted *p*-bromoanisole (**5.50**) into *p*-anisaldehyde (**5.51**) in 25% yield with 16% of anisole (**5.52**) as a byproduct (Table 24, page 137, Entry 1) in chamber 2, indicating that syngas is being developed from diglyme.

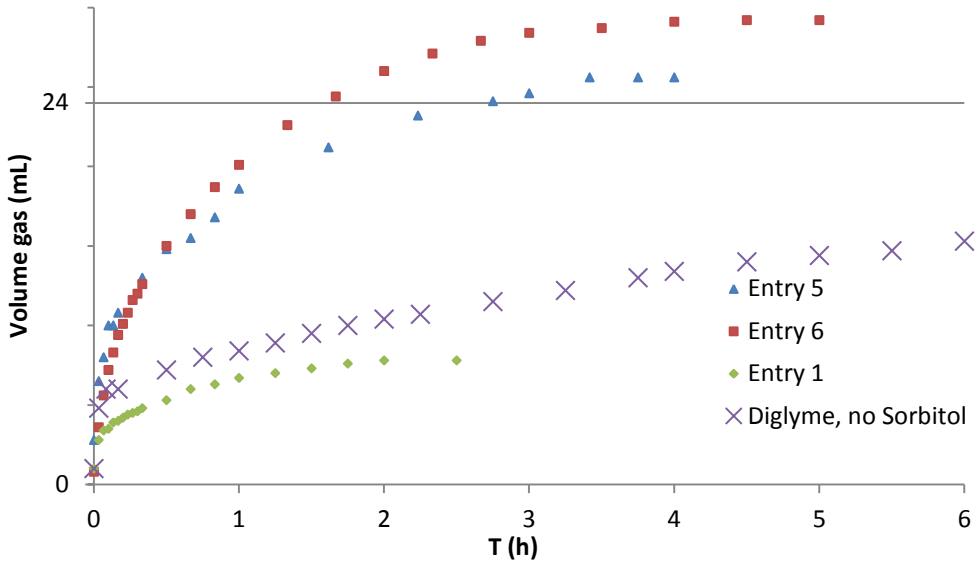
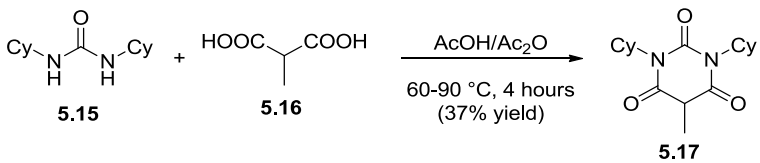


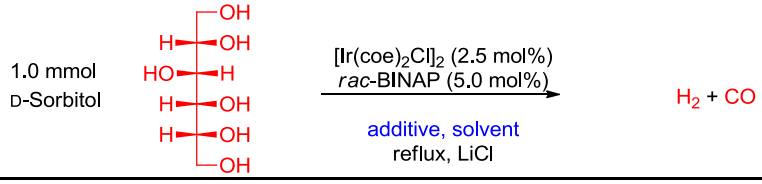

**Figure 33 - Gas development by iridium catalysis (entries from Table 21)**

The amount of gas developed was still too low to be applied in the reductive carbonylation and a reason could be the low solubility of the carbohydrate in the solvents. Various additives were tried to see if any improvement could be made. Borane and stannane compounds could reversibly attach to *cis*-diols and thereby make the compounds more lipophilic. The additives, $PhB(OH)_2$ and $Bu_2SnO$ did not improve the gas development (Table 22, Entry 1-3). Barbiturate **5.17** (synthesized from urea **5.15** and methylmalonic acid (**5.16**) (Scheme 55)) was also tried as an additive, as it might serve as an anchor as described in section 5.2.3, but no improvement in the amount of syngas was observed (Table 22, Entry 5).




**Scheme 55 - Preparation of barbiturate 5.17**

**Table 22 - Gas development, additives screening**




| Entry | additive (equiv.) | solvent ($H_2O$/ppm[a]) | $V_{max}$ (mL)[b] | T (h)[c] |
|---|---|---|---|---|
| 1 | $PhB(OH)_2$ (1.0) | mesitylene (150) | 15.3 | 4 |
| 2 | $PhB(OH)_2$ (1.0) | diglyme (200) | 6.0 | 0.5 |
| 3 | $Bu_2SnO$ (1.0) | mesitylene (150) | 4.0 | 0.5 |
| 4 | TBACl (0.10) | mesitylene (150) | 9.2 | 3.5 |
| 5[d] | **5.17** (0.20) | diglyme (108) | 17.2[e] | 6.5[e] |

a) $H_2O$ content measured by Karl Fischer instrument prior to reaction. b) Volume of gas where no further gas development is observed. c) Reaction time where $V_{max}$ is reached. d) D-sorbose used instead of D-sorbitol e) Slow gas development still occurring.

To test whether the standard dehydrogenative decarbonylation on D-sorbitol developed a sufficient amount of syngas, the conditions were applied to the two-chamber system coupled to the reductive carbonylation. This method converted *p*-bromoanisole (**5.50**) into *p*-anisaldehyde (**5.51**) in 3% yield with 6% of anisole (**5.52**) as byproduct (Table 24, page 137, Entry 2).

### 5.2.3 Anchor strategy

It seems that utilizing raw carbohydrates as a syngas source was an uphill battle and therefore this section describes work on attaching carbohydrates to a lipophilic anchor. A lipophilic anchor might force the polyols into solution, thereby making the syngas development possible. Potentially the anchor could be reused making the atom economy acceptable. The optimal attachment point of the anchor was a carbon with an acidic proton and therefore attachment of the carbohydrate aldoses was possible under basic conditions.

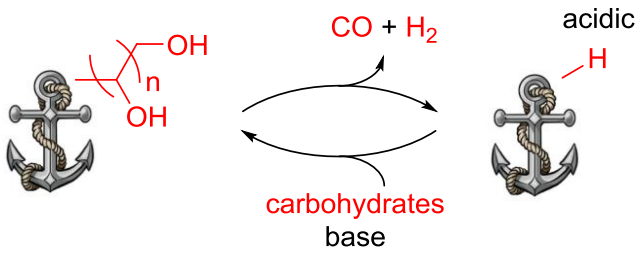
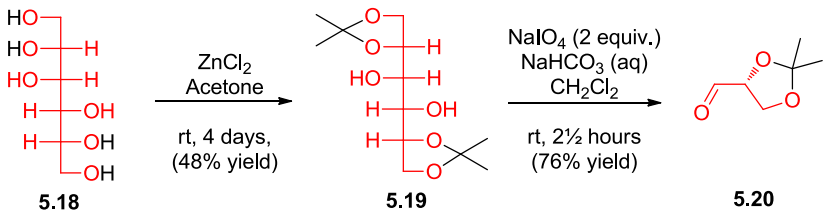



**Figure 34 – Anchor strategy**

### *Aldehydes and aldoses*

Monools could be prepared by addition of the anchor to formaldehyde and were ideal substrates for the elucidation of the late dehydrogenative carbonylation steps. Vicinal diols could be obtained by the addition to glycolaldehyde dimer. This dimer was convenient for optimizing the conditions for the attachment to the anchor which might be used for longer unprotected carbohydrate aldoses. If base stable protecting groups were necessary in the preparation of triol substrates, 2,3-*O*-isopropylidene-D-glyceraldehyde (**5.20**) could be employed and the aldehyde **5.20** was easily prepared from 1,2;5,6-di-*O*-isopropylidene-D-mannitol (**5.19**) in a yield of 76% (Scheme 56). Diol **5.19** was prepared from D-mannitol (**5.18**) in a yield of 48% and the reaction also furnished 1,2;3,4;5,6-tri-*O*-isopropylidene-D-mannitol in a yield of 25%. The reaction might have produced a higher yield of diol **5.19** if a shorter reaction time was applied. 2,3;5,6-Di-*O*-isopropylidene-D-mannofuranose (**5.21**) was prepared from D-mannose in a yield of 83% and can be used for the synthesis of hexaols.




**Scheme 56 – Preparation of 2,3-*O*-isopropylidene-D-glyceraldehyde**

### *Barbiturate anchors*

*N,N'*-Dimethylbarbiturate (**5.22**) has a $pK_a$ value of 4.7[250] and is able to react with carbohydrates in aqueous media.[251] Due to the acidity of the second proton, only the sodium enolate was isolated and the following acetylation furnished either the eliminated product **5.53** or the cyclized product **5.54**. Therefore, in our barbiturate design, a methyl group was added. Cyclohexyl groups were used instead of methyl groups for making the compound more lipophilic. We measured the $pK_a$ value of barbiturate **5.17** to 6.8 in aqueous media and therefore it should still be possible to attach carbohydrates in aqueous media.

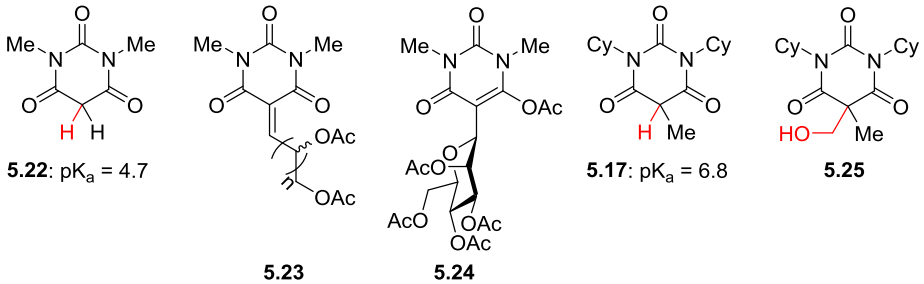


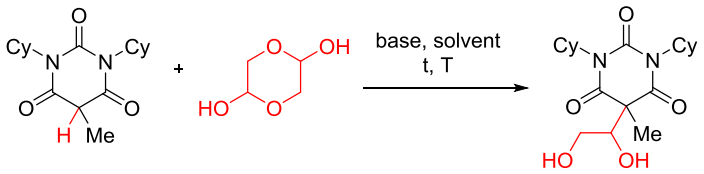

**Figure 35 – Barbiturate anchors**

The monool **5.25** was easily prepared from barbiturate **5.22**. Applying the dehydrogenative decarbonylation conditions also rapidly converted the monool **5.25** back to the barbiturate **5.22** in a clean reaction. Thereafter, the formation of the diol **5.27** from barbiturate **5.22** and glycolaldehyde dimer (**5.26**) was optimized (Table 23). The reaction barely converted any of barbiturate **5.22** in $H_2O$, probably due to the low solubility of the starting material (Table 23, entry 1-2). Performing the reaction in dioxane worked decently and the optimal conditions employed sodium bicarbonate as base at 50 °C (Table 23, entry 4).

Experiments to attach a carbohydrate were also attempted. However, applying these conditions on barbiturate **5.22** with D-xylose did not furnish any product. A stability test of diol **5.27** performed in refluxing mesitylene or diglyme, showed decomposition of diol **5.27**. Due to the acidity of the barbiturate, the retro aldol reaction might have

occurred for both the carbohydrate attachment and the stability test. As a consequence, no further work with barbiturate anchors was performed.

**Table 23 – Formation of barbiturate diol 5.27**



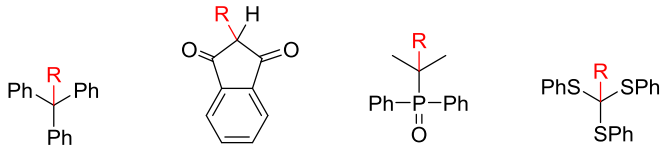

**5.22** **5.26** **5.27**

| entry | solvent | base | Equiv. **5.26** | pH[a] | t (°C) | T (h) | yield[b] |
|---|---|---|---|---|---|---|---|
| 1 | $H_2O$ | - | 0.5 | 6 | rt | | -[c] |
| 2 | $H_2O$ | $NaHCO_3$ | 0.5 | 9 | rt | | low[d] |
| 3 | dioxane | $NaHCO_3$ | 0.5 | 8 | 50 | 18 | 16% |
| 4 | dioxane | $NaHCO_3$ | 1.0 | 8 | 50 | 24 | 58% |
| 5 | dioxane | KOH | 0.5 | 8 | rt | 20 | 40% |
| 6 | dioxane | KOH | 1.0 | 8 | 50 | 24 | -[e] |
| 7 | dioxane | $K_2CO_3$ | 1.0 | 9 | 50 | 40 | 34% |
| 8 | DMF | $K_2CO_3$ | 1.0 | 9 | 50 | 24 | - |

a) pH measured by litmus paper. b) Isolated yield based on barbiturate **5.22**. c) No reaction observed by TLC-analysis. d) Low amount of product observed by crude $^1$H-NMR-spectroscopy. e) Byproduct formed, not isolated.

### *Trityl, indandione, isopropylphosphine oxide and tris(phenylthio)methane anchors*

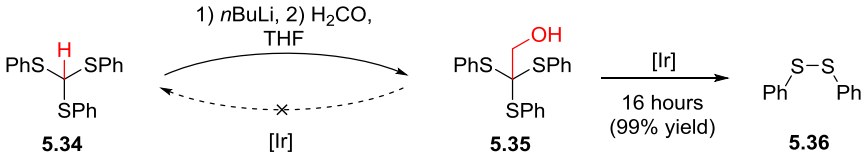
Additional anchors were attempted (Figure 36) and in these cases the monools from the corresponding anchors were prepared.



R = H, **5.28** **5.30** **5.32** **5.34**
R = $CH_2OH$, **5.29** **5.31** **5.33** **5.35**

**Figure 36 – Anchors attempted**

The reaction of deprotonated triphenylmethane (**5.28**) ($pK_a$ = 30.6)[252] with paraformaldehyde furnished 2,2,2-triphenylethanol (**5.29**). However, the dehydrogenative decarbonylation proceeded too slowly on the latter compound to be of any use. The low rate was probably due to steric hindrance. Under basic conditions, the nucleophilic carbon in 1,3-indandione (**5.30**) reacts with a ketone in another molecule of 1,3-indandione.[253] The prepared monool **5.33** derived from isopropyldiphenylphosphine oxide (**5.32**) gave an impure reaction upon treatment with the iridium catalyst. From tris(phenylthio)methane (**5.34**), the corresponding monool **5.35** was prepared. Treating **5.35** with the iridium catalyst did not furnish the desired dehydrogenative decarbonylation sequence. Instead 0.99 mmol diphenyl disulfide (**5.36**) was prepared from 1.00 mmol monool **5.35** (Scheme 57).

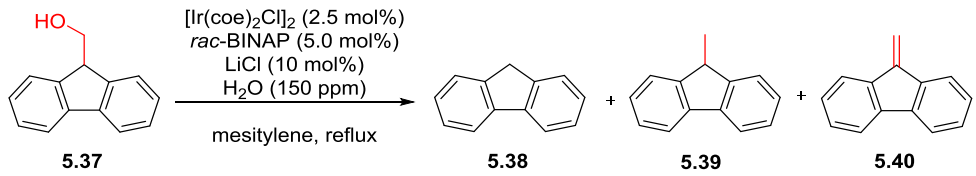



**Scheme 57 - Formation and iridium catalysis on 2,2,2-tris(phenylthio)ethane**

To decipher the origin of diphenyl disulfide (**5.36**), control experiments were performed. An experiment with the the iridium catalytic system on tris(phenylthio)methane (**5.34**) did not give diphenyl disulfide (**5.36**). Normally thiols can be oxidized into disulfides[254] and heating thiophenol with and without iridium catalyst suggested that iridium also catalyzes this oxidation.

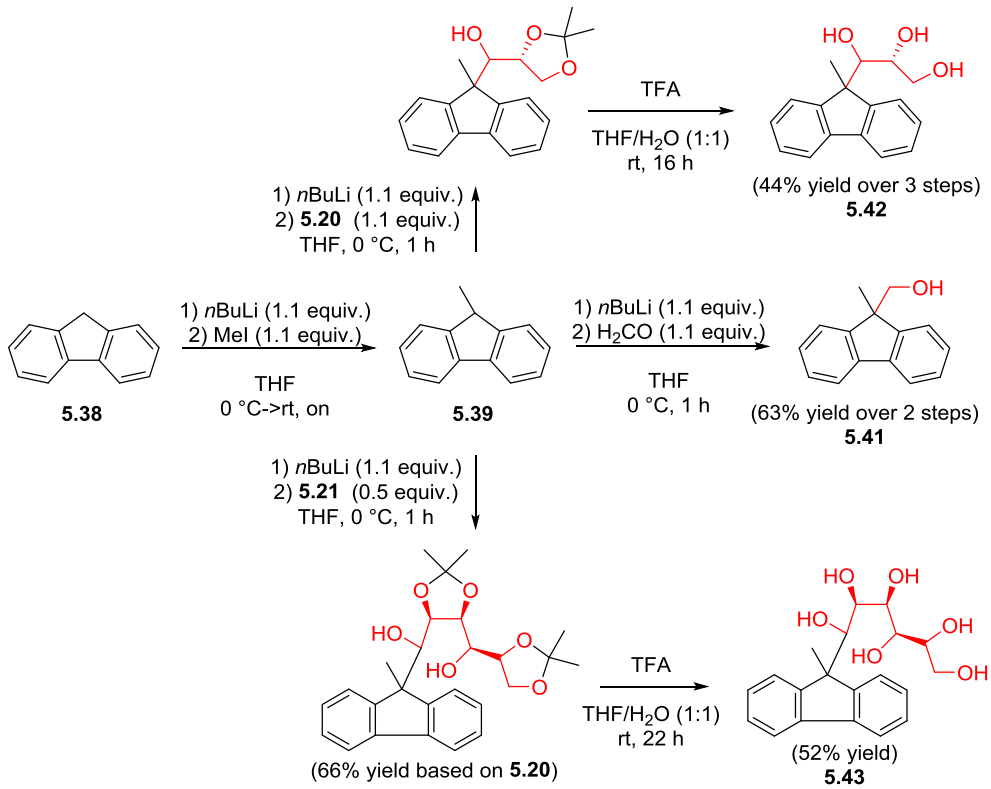
### *Fluorene anchors*

Due to aromatic stabilization of the anion, fluorene has a pKa value of 22.6, and hence fluorene would be a promising anchor.[252] Upon subjecting the commercially available 9-hydroxymethylfluorene (**5.37**) to the iridium catalyst, the dehydrogenative decarbonylation was not the only reaction occurring since a significant amount of 9-methylfluorene (**5.39**) and 9-methylenefluorene (**5.40**) were also formed besides fluorene (**5.38**) (Scheme 58)**.** The latter product originates from elimination of monool **5.37** and 9-methylfluorene (**5.39**) probably arises from hydrogenation of the methylene double bond in **5.40**.




**Scheme 58 – Dehydrogenative decarbonylation of 9-hydroxymethyl fluorene**

Following this result it was decided that the anchor design should not contain an additional proton on the attachment carbon. 9-Chlorofluorene and 9-fluorofluorene anchors were prepared but were not feasible as an anchor. 9-Methylfluorene (**5.39**) was prepared by deprotonation of fluorene (**5.38**) with *n*BuLi followed by a methylation with methyl iodide (Scheme 59). Deprotonating **5.39** with *n*BuLi and subsequently adding paraformaldehyde resulted in the fluorene monool **5.41** in 63% yield from fluorene. The fluorene triol **5.42** and fluorene hexaol **5.43** were also prepared in similar manner although deprotection of the isopropylidene group was required.




**Scheme 59 – Attachment to the methyl fluorene anchor 5.39**

When applying the fluorene monool **5.41** to the dehydrogenative decarbonylation conditions in mesitylene the conversion rate was too slow to be conveniently coupled with the reductive carbonylation. Furthermore, according to GC analysis, the aldehyde was accumulated which means that the gas mixture had a larger amount of $H_2$ versus CO. The gas development from the dehydrogenative decarbonylation of monool **5.41** performed in diglyme did not even produce one equivalent of gas after 24 hours and the rate was slower than the reaction in diglyme without any added alcohol (Figure 37). The gas development from the fluorene triol **5.42** and hexaol **5.43** were also established, as the lesser steric requirements around the terminal alcohols result in a faster reaction. The highest amount of gas was found by the fluorene triol **5.42** in diglyme, but the amount is not much higher than two equivalents of gas. In mesitylene the fluorene triol **5.42** produced only a little more than one equivalent

after 20 hours and the progression seemed to have stopped (full conversion would have produced 6 equivalents).

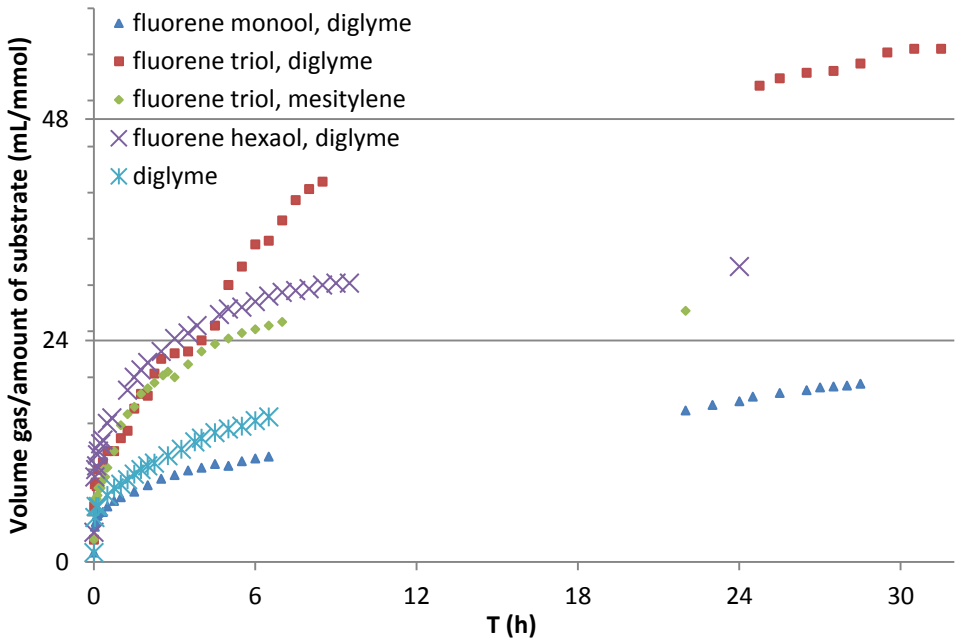
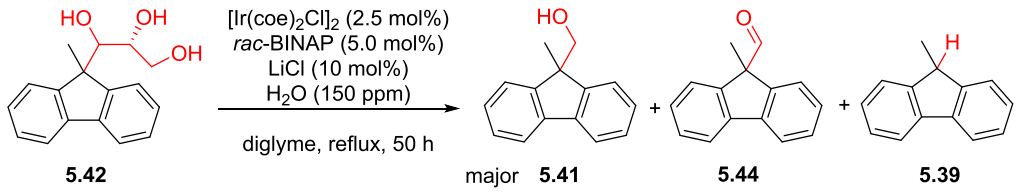



**Figure 37 - Gas development of fluorene alcohols**

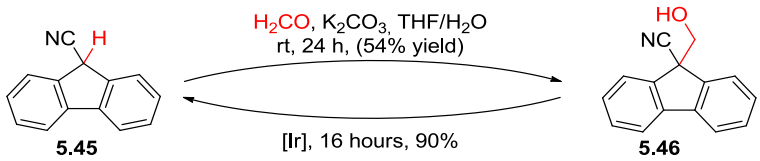
According to a GC chromatogram, the product distribution FROM the dehydrogenative decarbonylation of the triol **5.42** after gas monitoring for 50 hours consisted mainly of the fluorene monool **5.41**, the fluorene aldehyde **5.44** and 9-methylfluorene (**5.39**) (Scheme 60). In an attempt to monitor the reaction over time it was observed that a mixture of products already was observed after 10 minutes of reaction time. Furthermore, in a stability test without the iridium catalyst, decomposition of the fluorene triol **5.42** and hexaol **5.43** were observed.




**Scheme 60 - Iridium catalysis on fluorene triol 5.42**

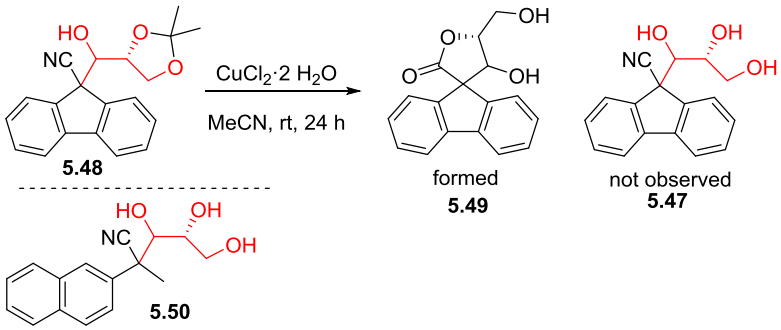
To determine if any syngas was formed in the reaction, the fluorene triol **5.42** was subjected to the two-chamber system. A low yield of the aldehyde was produced in chamber 2 and the selectivity was poor (Table 24, page 137, Entry 3). In addition, the methyl ester was produced indicating that methanol might have been present. Some syngas was produced although it was not obvious from what compound it originated.

9-Cyanofluorene (**5.45**) was synthesized as to further investigate potential anchors. **5.45** was converted into 9-cyano-9-hydroxymethylfluorene (**5.46**) and performing the dehydrogenative decarbonylation of this compound resulted in an isolated yield of 90% of **5.45** after 16 hours (Scheme 61). This is a lot faster than by employing 9-methylfluorene (**5.39**) as described *vide supra*.




**Scheme 61 - 9-Cyanofluorene anchor**

Attempts to obtain the cyano triol **5.47** failed. Under the conditions where the isopropylidene group was removed, an unexpected cyclization occurred from **5.48** and the lactone **5.49** was formed (Scheme 62).




**Scheme 62 - Formation of lactone 5.49, triol 5.50**

Triol **5.50** was prepared instead and employing the dehydrogenative decarbonylation conditions gave a 65% yield of 2-(2-naphthyl)propanenitrile (**5.51**) after 16 hours. However, employing triol **5.50** in the two-chamber system as a syngas source in chamber one did not convert any of the 2-bromonaphthalene (**2.10**) into the corresponding aldehyde **2.11** in chamber 2 (Table 24, page 137, Entry 4).

The triol **5.50** was too unstable to be used as a syngas source and the decomposition was thought to be following one or both of two pathways (Figure 38). A retro aldol mechanism and a dehydrogenation followed by an elimination pathway were both plausible. A similar explanation to the latter pathway was also observed from ruthenium catalysis on 1,3-diols as have been reported by Monrad and Madsen.[255]

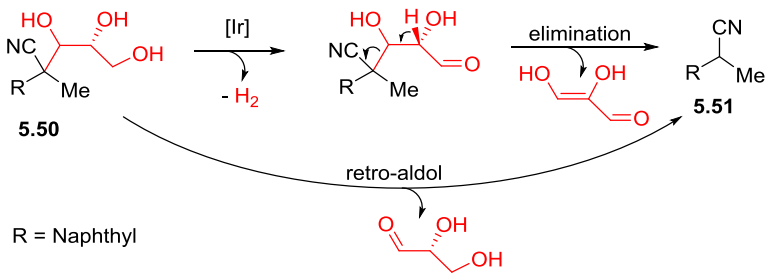


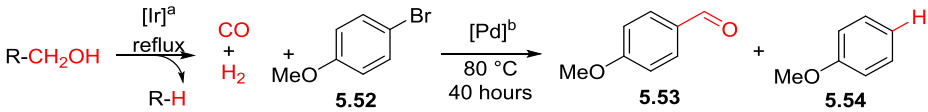

**Figure 38 - possible pathways for the decomposition of triol 5.50**

Following these disappointing results, no further work was performed on the anchor strategy.

### 5.2.4 Screening simple primary alcohols as syngas source

Primary alcohols are very common and they are present in almost every organic laboratory. Furthermore, they are in general bench stable and many are cheap. The screening for the optimal syngas source continued with substrates that would produce no products besides the evolved syngas. In the two-chamber system, paraformaldehyde in chamber one did produce some *p*-anisaldehyde (**5.53**) in chamber 2 (Table 24, Entry 5). A significant amount of methyl *p*-anisate was also produced and for that reason increasing the amount of the syngas source would not have helped. Ethylene glycol worked though it also produced a comparable low yield of the aldehyde **5.53** and the selectivity was poor (Table 24, Entry 6). Glycerol did not produce any aldehyde **5.53** (Table 24, Entry 7).

**Table 24 – Screening for the optimal syngas source in the two chamber system by using no waste sources.**

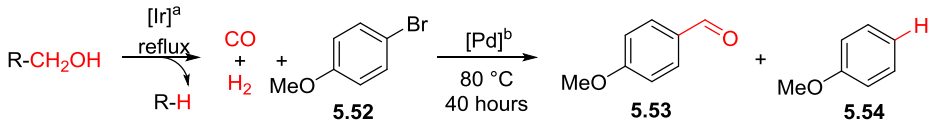



| Entry | Syngas source | equiv. –OH | Conv.[c] **5.52** | Yield[c] **5.53** | Yield[c] **5.54** |
|---|---|---|---|---|---|
| 1 | diglyme (solvent) | - | 41% | 25% | 16% |
| 2 | D-Sorbitol | 1.5 | 9% | 3% | 6% |
| 3[d] | Triol **5.50** | 1.5 | 27% | 12% | 10%[e] |
| 4[d] | Triol **5.50** | 1.5 | 3% | <0.1% | 3% |
| 5 | paraformaldehyde | 1.0 | 37% | 10% | 5%[f] |
| 6 | ethylene glycol | 2.0 | 97% | 42% | 44%[g] |
| 7[h] | Glycerol | 2.0 | - | 0% | - |

a) Syngas formed in chamber 1: alcohol (listed equiv.), $[Ir(cod)Cl]_2$ (2.5 mol%), *rac*-BINAP (5.0 mol%), LiCl (25 mol%) and mesitylene (2.0 mL, contains 150 ppm $H_2O$). b) Reductive carbonylation performed in chamber 2: *p*-bromoanisole (1.0 mmol), $Pd(Oac)_2$ (5.0 mol%), CataCXium A (10 mol%), TMEDA (2 equiv.) and toluene (2.0 mL). c) Conversion and yields determined by GC chromatogram from chamber 2 using standard curves of the compounds. d) 2-Bromonaphthalene used instead of *p*-bromoanisole, corresponding products formed. e) Methyl 2-naphthoate also produced in around 5% GC yield. f) Methyl *p*-anisate also produced in 22%. g) Methyl *p*-anisate also produced in about 8%. h) Reaction time was 64 h

It was apparent that none of the employed substrates in Table 24 produced satisfactory results in chamber two. Therefore, the following work employed simple primary alcohols despite that byproducts is being formed in chamber one. 2-Naphthylethanol was used in the optimization of the reductive carbonylation of 2-bromonaphthalene (**5.10)** and the same reaction conditions also converted a decent amount of *p*-bromoanisole (**5.50)** (Table 25, entry 1).

**Table 25 - Screening for the optimal syngas source in the two chamber system by using monools.**




| Entry | Syngas source | equiv. –OH | Conv.[c] **5.52** | Yield[c] **5.53** | Yield[c] **5.54** |
|---|---|---|---|---|---|
| 1 | 2-napthylethanol | 1.0 | 69% | 59% | 10% |
| 2 | | 2.0 | >99% | 93% (74%)[d] | 7% |
| 3 | 2-phenylethanol | 1.0 | 13% | 6% | 7% |
| 4 | | 2.0 | 35% | 27% | 8% |
| 5 | ethanol 99% | 3.0 | 77% | 37% | 34%[e] |
| 6 | pentan-1-ol | 2.0 | 89% | 78% | 11% |
| 8 | heptan-1-ol | 2.0 | 82% | 75% (57%)[d] | 7% |
| 9 | decan-1-ol | 1.0 | 28% | 21% | 7% |
| 10 | dodecan-1-ol | 2.0 | 85% | 77% | 8% |
| 11 | BnOH | 1.0 | 57% | 44% | 13% |
| 12 | | 2.0 | >99% | 83% | 18% |

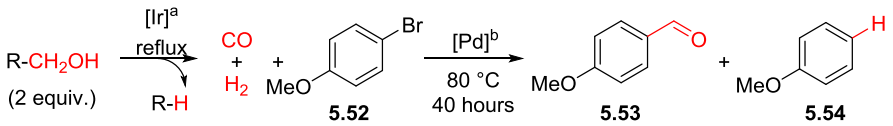
a) Syngas formed in chamber 1: alcohol (listed equiv.), $[Ir(cod)Cl]_2$ (2.5 mol%), *rac*-BINAP (5.0 mol%), LiCl (25 mol%) and mesitylene (2.0 mL, contains 150 ppm $H_2O$). b) Reductive carbonylation performed in chamber 2: *p*-bromoanisole (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), CataCXium A (10 mol%), TMEDA (2 equiv.) and toluene (2.0 mL). c) Conversion and yields determined by GC chromatogram from chamber 2 using standard curves of the compounds. d) Isolated yield in parentheses. e) Ethyl *p*-anisate also produced in about 5%.

One equivalent of syngas donor was not sufficient to convert bromide **5.52** completely as the electron rich system makes the oxidative addition to bromide **5.52** slower. When 2 equivalents of the syngas donor was applied, full conversion of bromide **5.52** was obtained and with a good selectivity favoring aldehyde **5.53**, which was isolated in 74% yield (Table 25, entry 2). 2-Phenylethanol and ethanol did not

produce a satisfying amount of aldehyde **5.53** (Table 25, entry 3-5). In the ethanol reaction, a small quantity of ethyl *p*-anisate was also produced. The aliphatic primary alcohol produced a decent selectivity favoring aldehyde **5.53** although none of these reductive carbonylations went to completion (Table 25, entry 6-10). Benzylalcohol fully converted **5.52** though the reaction suffered from a less satisfactory selectivity (Table 25, entry 11-12). This was most likely because benzaldehyde accumulated in the syngas producing chamber causing the initial release rate of CO to be a lot lower than the release rate of $H_2$.

Some diols were also applied as a syngas source and the chains with 5 carbons and lower did not produce a satisfying conversion of bromide **5.52** (Table 26, entry 1-4). For the butane and pentane substrates, it was theoretically possible to cyclize the diols into THF and THP respectively or after the dehydrogenative step cyclize into the corresponding cyclic heniacetals. The longer hexane- and dodecane-diols fully converted bromide **5.52** and the selectivity for aldehyde **5.53** was good (Table 26, entry 5, 7). It appeared that these diols perform better compared to their monool counterpart. A study of the reason for this has not been performed. Tetraethylene glycol converted bromide **5.52** slowly and tetraethylene glycol suffered from decomposition and the ether oxygen might coordinate to the iridium complex, consequently slowing the reaction down as described in section 4.2.5 (Table 26, entry 6).

**Table 26 - Screening for the optimal syngas source in the two chamber system by using diols.**

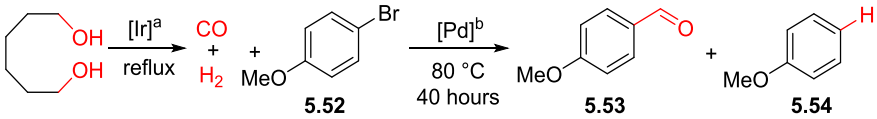



| Entry | Syngas source | Conv.[c] **5.52** | Yield[c] **5.53** | Yield[c] **5.54** |
|---|---|---|---|---|
| 1 | 2-methylpropane-1,3-diol | 53% | 45% | 8% |
| 2 | neopentyl glycol | 24% | 17% | 7% |
| 3 | butane-1,4-diol | 42% | 25% | 17% |
| 4 | pentane-1,5-diol | 32% | 17% | 17% |
| 5 | hexane-1,6-diol | >99% | 92% | 8% |
| 6 | tetraethylene glycol | ~41% | ~18% | ~5%[d] |
| 7 | dodecane-1,12-diol | >99% | 93% (66%)[e] | 7% |

a) Syngas formed in chamber 1: alcohol (listed equiv.), $[Ir(cod)Cl]_2$ (2.5 mol%), *rac*-BINAP (5.0 mol%), LiCl (25 mol%) and mesitylene (2.0 mL, contains 150 ppm $H_2O$). b) Reductive carbonylation performed in chamber 2: *p*-bromoanisole (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), CataCXium A (10.0 mol%), TMEDA (2 equiv.) and toluene (2.0 mL). c) Conversion and yields determined by GC chromatogram from chamber 2 using standard curves of the compounds. d) Unknown byproduct formed, not isolated. GC yields in this entry row are not fully accurate. e) Isolated yield in parentheses.

Hexane-1,6-diol, dodecane-1,12-diol and 2-napthylethanol produced similar results in the two chamber setup, but since hexane-1,6-diol was the cheapest of the three diols it was chosen as a syngas source for further optimization. Hexane-1,6-diol is produced commercially from the hydrogenation of adipic acid and is industrially used for production of polyesters and polyurethans. Upon screening for the most optimal amount of the diol it was found that one equivalent of the diol in the gas producing chamber *versus* one equivalent of bromide **5.52** in the gas consuming chamber resulted in the best selectivity (Table 27, entry 3) and full conversion. With a lower amount, full conversion was not achieved within 40 hours (Table 27, entry 1-2). With a higher amount, the selectivity for **5.53** dropped gradually (Table 27, entry 6-7). Lowering the catalyst concentration in chamber one decreased the conversion rate and also resulted in a less satisfactory selectivity in chamber two (Table 27, entry 4). Employing diglyme as a solvent in chamber one instead of mesitylene severely decreased the selectivity in chamber two (Table 27, entry 5).

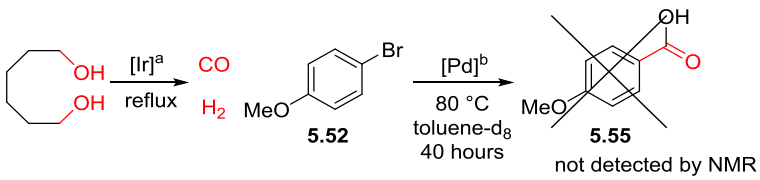
**Table 27 - Screening for the optimal syngas source in the two chamber system using by adjusting the amount of hexane-1,6-diol.**




| Entry | equiv. –OH | Conv.[c] **5.52** | Yield[c] **5.53** | Yield[c] **5.54** |
|---|---|---|---|---|
| **1** | 1.0 | 18% | 13% | 5% |
| **2** | 1.5 | 25% | 16% | 10% |
| **3** | 2.0 | >99% | 92% | 8% |
| **4**[d] | 2.0 | 63% | 47% | 16% |
| **5**[e] | 2.0 | 92% | 47% | 38% |
| **6** | 3.0 | >99% | 85% | 15% |
| **7** | 4.0 | >99% | 63% | 37% |

a) Syngas formed in chamber 1: 1,6-hexanediol (listed equiv.), $[Ir(cod)Cl]_2$ (2.5 mol%), *rac*-BINAP (5.0 mol%), LiCl (25 mol%) and mesitylene (2.0 mL, contains 150 ppm $H_2O$). b) Reductive carbonylation performed in chamber 2: *p*-bromoanisole (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), CataCXium A (10.0 mol%), TMEDA (2 equiv.) and toluene (2.0 mL). c) Conversion and yields determined by GC chromatogram from chamber 2 using standard curves of the compounds. d) 1.0 mol% $[Ir(cod)Cl]_2$, 2.0 mol% rac-BINAP. e) Diglyme as solvent in chamber 1, also 8% methyl *p*-anisate produced.

During the optimization studies in the Skrydstrup group, they have transformed some of the aryl iodide into the corresponding carboxylic acid as a byproduct.[248] As the GC instrument in our department was not able to elute *p*-methoxybenzoic acid (**5.55**), NMR experiments of the crude mixture was performed to potentially detect *p*-methoxybenzoic acid (**5.55**). After 40 hours of reaction time using fully deuterated toluene as the solvent, no carboxylic acid signals were observed by $^{1}H$- and $^{13}C$-NMR spectroscopy experiments (Scheme 63).




**Scheme 63 - Test for detection of benzoic acid 5.55 by NMR**

The gas development from hexane-1,6-diol under the optimal conditions was established. The graph shows that the amount of gas developed corresponded to around 4 equivalents of gas (Figure 39). Although if the diol was fully converted, 5 equivalents of gaseous molecules would have been expected as butane is also a gaseous molecule at room temperature. The gas development was complete after about 10 hours using an iridium catalyst loading of 10 mol%.

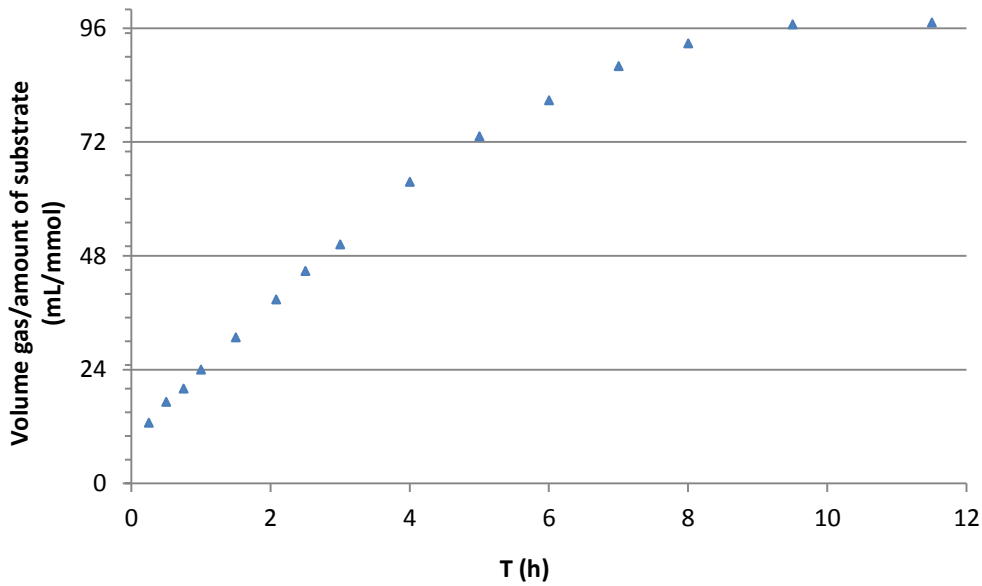
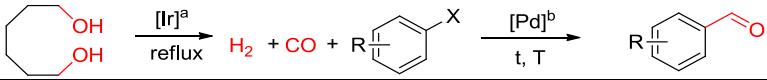


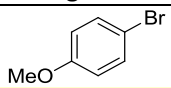
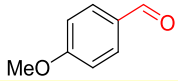
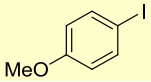
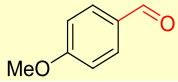
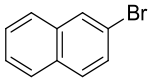
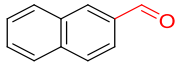
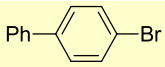
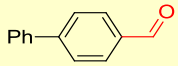
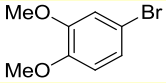
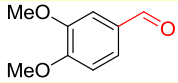
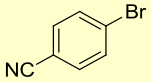
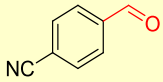
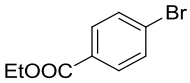
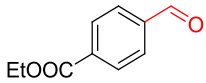
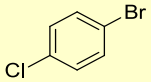
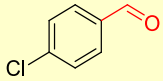
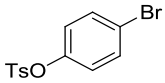
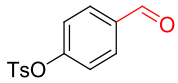

**Figure 39 - Gas development from 0.5 mmol of hexane-1,6-diol under the optimized conditions.**

### 5.2.5 Substrate Scope

Following the optimization of both reaction chambers in the two chamber system, a short substrate scope study was initiated. The two chamber system worked on both bromides and iodides (Table 28, Entry 1-2) in decent yields. Until now, 2-bromonaphthalene provided the highest yield of 79% (Table 28, Entry 3).

**Table 28 – Substrate scope study of the reductive carbonylation in the two chamber system.**



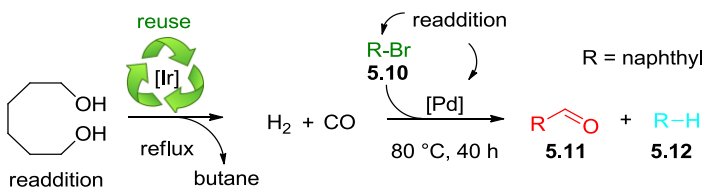

| Entry | Starting material | t (°C) | T (h) | Product | Isolated yield |
|---|---|---|---|---|---|
| 1[c] |  | 80 | 40 |  | 71% |
| 2 |  | 80 | 90 |  | 73% |
| 3 |  | 80 | 40 |  | 79% |
| 4 |  | 80 | 40 |  | 69% |
| 5 |  | 80 | 90 |  | 60% |
| 6 |  | 80 | 40 |  | 20% |
| 7 | | 60 | 90 | | 35% |
| 8 |  | 80 | 40 |  | 20% |
| 9 | | 60 | 90 | | 35% |
| 10 |  | 80 | 40 |  | 27% |
| 11 | | 60 | 90 | | 56% |
| 12 |  | 80 | 40 |  | 33% |
| 13 | | 60 | 114 | | 56% |

a) Syngas formed in chamber 1: hexane-1,6-diol (1.0 mmol), $[Ir(cod)Cl]_2$ (2.5 mol%), *rac*-BINAP (5.0 mol%), LiCl (25 mol%) and mesitylene (2.0 mL, contains 150 ppm $H_2O$). b) Reductive carbonylation performed in chamber 2: aryl halide substrate (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), CataCXium A (5.5-10.0 mol%), TMEDA (2 equiv.) and toluene (2.0 mL).

Bromobiphenyl and bromoveratrole afforded a slightly lower yield of their corresponding aldehydes (Table 28, Entry 4-5). The bromides with an electron withdrawing group in the para position all resulted in a low yield (Table 28, Entry 6, 8, 10 and 12). Analyzing the GC MS chromatograms before isolating the aldehydes in all these cases showed that full conversion of the bromides occurred. Also the only observed byproducts were the reductive dehalogenated products. According to the

Hammett plot made in the Beller Group, the reactions with the electron-poor aryl bromides, as a consequence of the electron withdrawing groups, have a comparably faster reductive carbonylation rate.[241] Performing the reductive carbonylation at 65 °C did not fully convert 2-bromonaphthalene (**2.10**) after 40 hours (Table 20, page 123, entry 6) although these substrates might be able to be fully converted with a longer reaction time. The Beller group also states that a lower reaction temperature results in a higher product selectivity favoring the aldehydes. Therefore, lowering the temperature even further on these substrates (at the cost of a longer reaction time) increased the selectivity significantly favoring the corresponding aldehydes (Table 28, Entry 7, 9, 11 and 13).

In addition it was found that the catalytic system in chamber one could be reused for more reactions in chamber two. After a reaction of 2-bromonaphthalene (**5.10**) was completed, the entire content of chamber two was removed, replaced with a new reductive carbonylation system setup and additional hexane-1,6-diol was added to chamber one (Scheme 64). This resulted in full conversion in 7 consecutive reactions and could potentially go further on (Figure 40). Though reducing the iridium concentration in chamber one from 5 mol% to 2 mol% reduced the conversion rate in chamber two (Table 27, page 141, entry 4), this reuse of the catalytic system could be a procedure for applying the relatively expensive metal iridium more efficiently.




**Scheme 64 - Reusing the reuse of the iridium catalyst for reductive carbonylation of 2-bromonaphthalene 5.10**

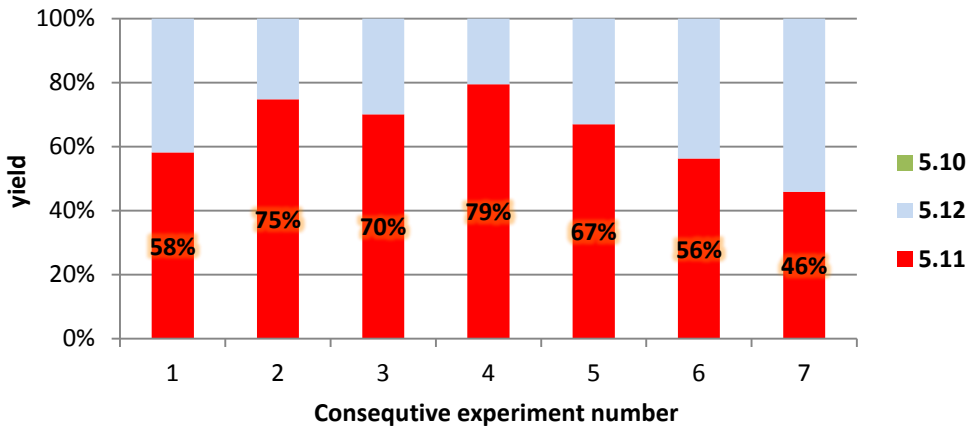
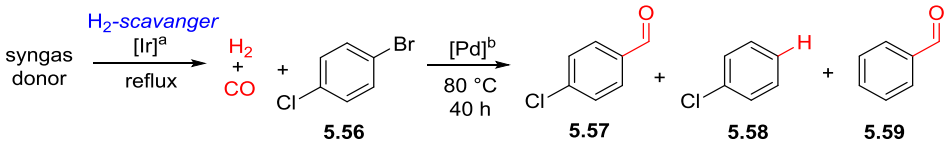



**Figure 40 - Data for the reuse of the iridium catalyst for reductive carbonylation of 2-bromonaphthalene (5.10)**

A number of possible $H_2$-scavangers were added to chamber one to test whether this would improve the yield of the reductive carbonylation by lowering the amount of $H_2$ as compared to CO. 4-Chlorobromobenzene (**5.56**) was chosen as the substrate in chamber two since the product mixture of 4-chloroaldehyde (**5.57**), chlorobenzene (**5.58**), benzaldehyde (**5.59**) and bromide **5.56** are all separated in the GC MS chromatogram. The selectivity for 4-chloroaldehyde (**5.57**) was increased by using 0.5 equivalent of norbornene (Table 29, Entry 2). A large amount of $H_2$ was scavenged using 1.0 equivalent of norbornene and therefore the amount of $H_2$ liberated out of chamber one was too low to make the reductive carbonylation work (Table 29, Entry 3). Furthermore, an obtained GC MS chromatogram from chamber two indicated that ketone **5.60** was formed by the carbonylative Heck reaction.[256,257] Some norbornene must have diffused from chamber one into chamber two under these conditions. Using 0.5 equivalents of diphenylacetylene resulted in the best selectivity (Table 29, Entry 4). Benzophenone did not seem to have any effect on the reaction (Table 29, Entry 5). Full conversion from tetrahydropyranol could potentially provide twice the amount of CO as compared to $H_2$. Using 3 equivalents of this syngas donor also furnished a slightly better selectivity for **5.57** (Table 29, Entry 6). 2,3,4-Tri-*O*-acetyl-D-xylopyranose (**5.61**) as a syngas donor did not convert any of the 4-Chlorobromobenzene (**5.56**) in chamber 2 (Table 29, Entry 8).

**Table 29 – Reductive carbonylation in the two chamber system by using excess CO than $H_2$.**



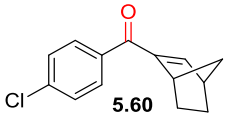

| Entry | syngas donor<br>*Scavanger* | equiv. donor<br>*scavenger* | Conv.[c]<br>**5.56** | Yield<br>**5.57** | Yield<br>**5.58** | Yield<br>**5.59** |
|---|---|---|---|---|---|---|
| 1 | hexane-1,6-diol | 1 | >99% | 55% | 36% | 9% |
| 2[d] | hexane-1,6-diol<br>*norbonene* | 1<br>*0.50* | 96% | 73% | 22% | 1% |
| 3 | hexane-1,6-diol<br>*norbonene* | 1<br>*1.0* | 14% | 7% | 7% | 0% |
| 4 | hexane-1,6-diol<br>*diphenylacetylene* | 1<br>*0.50* | 55% | 51% | 4% | 0% |
| 5 | hexane-1,6-diol<br>*benzophenone* | 1<br>*0.50* | >99% | 57% | 37% | 6% |
| 6 | tetrahydropyranol | 3.0 | >99% | 67% | 29% | 4% |
| 7 | tetrahydropyranol | 1.5 | 37% | 15% | 22% | 0% |
| 8 | **5.61** | 1.0 | 0% | 0% | 0% | 0% |

a) Syngas formed in chamber 1: alcohol/aldose (listed equiv.), $H_2$-scavanger (listed equiv.) $[Ir(cod)Cl]_2$ (2.5 mol%), *rac*-BINAP (5.0 mol%), LiCl (25 mol%) and mesitylene (2.0 mL, contains 150 ppm $H_2O$). b) Reductive carbonylation performed in chamber 2: 4-Chlorobromobenzene (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), CataCXium A (5.5 mol%), TMEDA (2 equiv.) and toluene (2.0 mL). c) Conversion and yields determined by GC chromatogram from chamber 2 using standard curves of the compounds. d) Carbonyl Heck cross-coupling product also formed

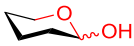
norbonene

PhC≡CPh

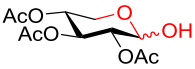
diphenylacetylene



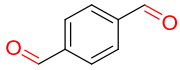

**5.60**




tetrahydropyranol




**5.61**

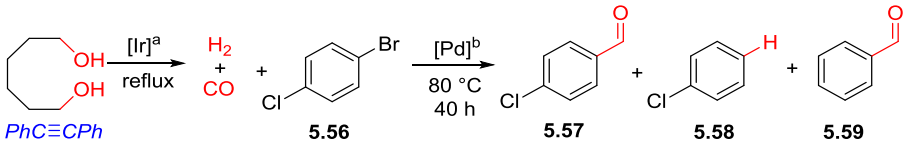



**5.62**

Another observation was that benzaldehyde (**5.59**) was formed in the reactions where the starting material **5.56** had been consumed. Not surprisingly, the palladium catalyst seems to convert the bromide moiety prior to the chloride. The 1,4-dialdehyde, teraphthalaldehyde (**5.62**) was not detected in any of the above reactions.

Diphenylacetylene provided the best selectivity among the studied scavengers and the next step was therefore to adjust the amount of hexane-1,6-diol and diphenylacetylene to provide the optimal conditions. All reactions in Table 30 were fully converted except in entry 4.

**Table 30 - Adjusting the equivalents of hexane-1,6-diol and diphenylacetylene in two chamber system.**




| Entry | diol equiv. | scavenger equiv. | yield[c] **5.55** | scavenged $H_2$ (equiv.)[d] | yield[c] **5.56** | yield[c] **5.57** |
|---|---|---|---|---|---|---|
| 1 | 1.0 | 0.10 | 65% | 0.18 | 27% | 7% |
| 2 | 1.0 | 0.25 | 71% | 0.49 | 25% | 4% |
| 3 | 1.0 | 0.33 | 87% | 0.55 | 12% | 2% |
| 4[e] | 1.0 | 0.50 | 51% | 0.77 | 4% | 0% |
| 5 | 1.5 | 0.33 | 80% | 0.54 | 14% | 6% |
| 6 | 2.0 | 0.33 | 69% | 0.56 | 23% | 9% |
| 7 | 4.0 | 0.33 | 70% | 0.57 | 20% | 11% |
| 8[f] | 6.0 | 0.33 | 53% | 0.59 | 32% | 7% |

a) Syngas formed in chamber 1: hexane-1,6-diol (listed equiv.), diphenylacetylene (listed equiv.) $[Ir(cod)Cl]_2$ (2.5 mol%), *rac*-BINAP (5.0 mol%), LiCl (25 mol%) and mesitylene (2.0 mL, contains 150 ppm $H_2O$). b) Reductive carbonylation performed in chamber 2: 4-Chlorobromobenzene (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), CataCXium A (5.5 mol%), TMEDA (2 equiv.) and toluene (2.0 mL). c) Conversion and yields determined by GC chromatogram from chamber 2 using standard curves of the compounds. d) $H_2$ scavenged determined by GCMS of chamber 1, from the conversion of diphenylacetylene into stilbene and bibenzyl. e) Same as Table 29 entry **4**. f) Teraphthalaldehyde (**5.62**) also formed in chamber 2 in about 8% GC yield

The optimal conditions were found to be 1.0 equivalent of hexane-1,6-diol and 0.33 mmol of scavenger (Table 30, entry 3). The amount of $H_2$ scavenged was estimated to be 0.55 equivalent meaning that a full conversion of hexane-1,6-diol would provide 2 equivalents of CO and 1.45 equivalents of $H_2$. Lowering the amount of scavenger or increasing the amount of the syngas source both decreased the selectivity for aldehyde **5.57**. Teraphthalaldehyde (**5.62**) was only observed when a high amount of hexane-1,6-diol was applied (Table 30, entry 8).

## 5.3 Conclusion and further perspectives

The syngas developed from the dehydrogenative decarbonylation of primary alcohols has been applied in the reductive decarbonylation of aryl bromides in a two chamber system. Work with this project is still in progress. The remaining work in this project consists of obtaining a substrate scope and getting isolated yields with the optimized system including the $H_2$ scavenger for the electron poor aryl bromides. Furthermore, monitoring the pressure during the reactions using different syngas sources could give an insight into the reaction progress. $^{13}$C-labeling experiments using a $^{13}$C syngas source would also confirm that the source of the CO originates from the alcohol.

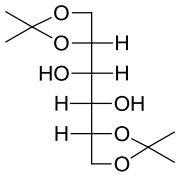
Also applying the syngas in the hydroformylation reaction as performed in the Andersson group will extend the application of the catalytic system even further.

## 5.4 Experimental

### 5.4.1 General methods

The same general methods as described in section 2.4.1 were followed. Furthermore, TMEDA was distilled into a flask with 4Å molecular sieves where it was stored until use. Toluene, acetone and $CH_2Cl_2$ were dried using 4Å molecular sieves. The $H_2O$ content of solvents were measured by a Karl Fischer instrument.

### 5.4.2 Preparation of 1,2;5,6-di-*O*-isopropylidene-D-mannitol (5.19)



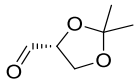
The preparation of 1,2;5,6-di-*O*-isopropylidene-D-mannitol was performed by following a procedure by Kuszmann *et al.* [258] Anhydrous zinc chloride (64 g, 0.54 mol) was dissolved in dry acetone (470 mL) by stirring at room temperature for 15 minutes. D-Mannitol (**5.18**) (21 g, 0.11 mol) was added and the reaction stirred at room temperature for four days. The solution was diluted with $CH_2Cl_2$ (400 mL) and cooled in ice/water bath. A solution of potassium carbonate (~100 g in 150 mL $H_2O$) was added slowly and the suspension stirred vigorously for 30 minutes. The slurry mixture was filtered and the white precipitate washed twice with $CH_2Cl_2$ (250 mL). Most of the solvent was removed under reduced pressure. The product mixture was diluted with $CH_2Cl_2$ and washed with $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated into white crystals. Recrystallization from heptane yielded the product 1,2;5,6-di-*O*-isopropyl-D-mannitol (**5.19**) (7.208 g, 0.027 mol, 25%) as white crystals.

***R*$_f$** = 0.24 (EtOAc/heptane 2:1)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 4.21 – 4.03 (m, 4H), 3.95 (dd, J = 8.1, 5.0 Hz, 2H), 3.71 (t, J = 6.4 Hz, 2H), 2.87 (d, J = 6.9 Hz, 2H), 1.38 (s, 6H), 1.32 (s, 6H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 109.5, 76.1, 71.1, 66.8, 26.9, 25.3

### 5.4.3 Preparation of (*R*)-isopropylideneglyceraldehyde 5.20

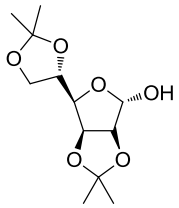


1,2;5,6-di-*O*-isopropylidene-D-mannitol **5.19** (9.558 g, 36.43 mmol) was dissolved in $CH_2Cl_2$ (100 mL). Saturated aqueous sodium bicarbonate (3.7 mL) was added followed by sodium periodate (16.05 g, 75.04 mmol). The reaction mixture was stirred at room temperature for 2.5 hours, and then filtered and concentrated. Vacuum distillation (90 °C, 185 mbar) yielded (*R*)-isopropylideneglyceraldehyde (**5.20**) (7.221 g, 55.37 mmol, 76%) as a colorless oil.

**$^{1}$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 9.75 – 9.55 (m, 1H), 4.41 – 4.24 (m, 1H), 4.20 – 3.90 (m, 2H), 1.42 (s, 3H), 1.35 (s, 3H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 201.8, 111.2, 79.9, 65.5, 26.2, 25.1

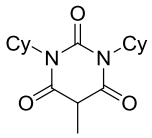
### 5.4.4 Preparation of 2,3;5,6-di-*O*-isopropylidene-α-D-mannofuranose (5.21)



D-Mannose (10.00 g, 55.51 mmol) was suspended in dry acetone (150 mL) and a few drops of $H_2SO_4$ were added and the reaction stirred at room temperature for two days. Saturated aqueous $NaHCO_3$ was added until the mixture was neutral according to litmus paper. Most of the solvent was removed under reduced pressure. The mixture was diluted with $CH_2Cl_2$ and washed with saturated aqueous $NaHCO_3$, brine and $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated into a colorless solid. Recrystallization from heptane/acetone/ethyl acetate afforded 2,3;5,6-di-*O*-isopropylidene-α-D-mannofuranose (**5.21**) (11.739 g, 45.1 mmol, 81%).

***R*$_f$** = 0.27 (EtOAc/heptane 2:1)
**mp** 121.4 – 122.9 °C (lit: 121-122)[259]
**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 5.37 (d, *J* = 1.7 Hz, 1H), 4.80 (dd, *J* = 5.9, 3.7 Hz, 1H), 4.61 (d, *J* = 5.9 Hz, 1H), 4.49 – 4.33 (m, 1H), 4.18 (dd, *J* = 7.1, 3.6 Hz, 1H), 4.13 – 4.00 (m, 2H), 3.06 (d, *J* = 2.2 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H)
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 112.8, 109.2, 101.4, 85.6, 80.3, 79.8, 73.4, 66.7, 27.0, 26.0, 25.3, 24.6
NMR data are in accordance with literature values.[260,261]

### 5.4.5 Preparation of *N,N'*-dicyclohexyl-5-methyl-barbituric acid (5.17)



*N,N'*-dicyclohexyl urea (8.75 g, 39.0 mmol) and 2-methyl-malonic acid (4.68 g, 39.6 mmol) were dissolved in glacial acetic acid (240 mL) and $Ac_2O$ (140 mL) was added slowly over 30 minutes at 60 °C. The temperature was raised to 90 °C and the mixture stirred for 4 hours. The solvent was removed under reduced pressure. Column chromatography (EtOAc/heptane 1:6) followed by recrystallization from heptane furnished *N,N'*-dicyclohexyl-5-methyl-barbituric acid (**5.17**) (4.40 g, 14.4 mmol, 37%) as white crystals.

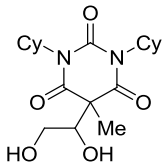
**mp** 99.3 – 101.0 °C

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 4.55 (tt, *J* = 12.2, 3.7 Hz, 2H), 3.40 (q, *J* = 7.3 Hz, 1H), 2.23 (qd, *J* = 12.3, 3.5 Hz, 4H), 1.91 – 1.75 (m, 4H), 1.72 – 1.50 (m, 9H), 1.45 – 1.15 (m, 6H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 169.3, 151.2, 55.6, 45.6, 29.5, 29.2, 26.5, 26.5, 25.3, 14.5

**pH** ($H_2O$): 6.8

### 5.4.6 Preparation of *N,N'*-dicyclohexyl-5-(1,2-dihydroxyethyl)-5-methyl-barbituric acid (5.27)



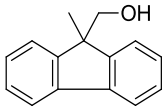

*N,N'*-Dicyclohexyl-5-methyl-barbituric acid (**5.17**) (153 mg, 0.50 mmol) and glycolaldehyde dimer (**5.56**) (61.8 mg, 0.51 mmol) were dissolved in dioxane (1.0 mL) and saturated aqueous $NaHCO_3$ was added until a pH value of around 8 was observed on litmus paper. The suspension was heated at 50 °C for 24 hours where the mixture was diluted with $CH_2Cl_2$. The organic phase was separated and washed with brine and $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated. Column chromatography (EtOAc/heptane 1:1) yielded *N,N'*-dicyclohexyl-5-(1,2-dihydroxyethyl)-5-methyl-barbituric acid (**5.27**) (106 mg, 0.29 mmol, 58%) as a white solid.

**mp** 177.3 – 178.5 °C (decomposes)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 6.74 (d, *J* = 7.1 Hz, 1H), 6.30 (d, *J* = 7.3 Hz, 1H), 5.22 (dd, *J* = 8.6, 6.8 Hz, 1H), 4.57 (dd, *J* = 9.4, 8.6 Hz, 1H), 4.45 (dd, *J* = 9.4, 6.8 Hz, 1H), 3.85 – 3.61 (m, 2H), 1.86 (t, *J* = 13.7 Hz, 4H), 1.78 – 1.53 (m, 6H), 1.48 (s, 3H), 1.45 – 1.07 (m, 10H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 169.1, 167.8, 154.3, 78.2, 66.7, 55.9, 49.2, 49.0, 32.7, 32.6, 25.49, 25.45, 24.89, 24.76, 24.73, 15.5

### 5.4.7 Preparation of (9-methyl-9H-fluoren-9-yl)methanol (5.41)

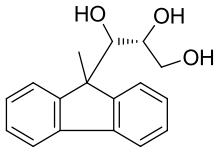


Fluorene (**5.38**) (10.40 g, 62.59 mmol) was dissolved in dry THF (100 mL) and cooled to 0 °C. *n*-Butyl lithium (27.5 mL, 2.5 M, 68.75 mmol) was added and the solution turned red. After 5 minutes, methyl iodide (4.40 mL, 70.7 mmol) was added and the mixture turned green. The reaction was allowed to reach room temperature and stirred overnight. The red solution was quenched with 1.0 M HCl (aq), extracted with diethyl ether and the organic phase was dried with $Na_2SO_4$, filtered and concentrated. Dry column chromatography yielded 9-methyl-9*H*-fluorene (**5.39**) (10.158 g) as the major component.

9-methyl-9*H*-fluorene (**5.39**) (2.108 g) was dissolved in dry THF and was cooled to 0 °C. *n*-Butyl lithium (5.0 mL, 2.5 M, 12.5 mmol) was added to the solution which turned red and after 5 minutes paraformaldehyde (379 mg, 12.6 mmol) was added and the reaction mixture was allowed to stir for 1 hour. The reaction was quenched with saturated aqueous ammonium chloride, and diluted with ethyl acetate, washed with saturated aqueous ammonium chloride and $H_2O$. The organic was dried with $MgSO_4$, filtered and concentrated into a yellow oil. Column chromatography (EtOAc/heptane) 1:2 afforded (9-methyl-9*H*-fluoren-9-yl)methanol (**5.41**) (1.708 g, 8.122 mmol, 63% over 2 steps) as a white solid.

***R*$_f$** = 0.32 (EtOAc/heptane 1:3)
**mp** 145.2 – 146.4 °C
**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.89 – 7.70 (m, 1H), 7.54 – 7.46 (m, 1H), 7.46 – 7.30 (m, 2H), 3.78 (s, 1H), 1.61 (s, 1H), 1.54 (s, 2H)
**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 149.5, 140.5, 127.7, 127.4, 123.4, 120.2, 70.0, 52.7, 21.1

### 5.4.8 Preparation of (2*R*)-1-(9-methyl-9*H*-fluoren-9-yl)propane-1,2,3-triol (5.42)



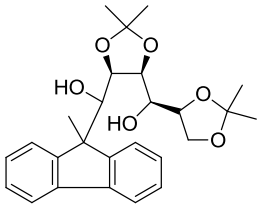

Fluorene (**5.38**) (4.138 g, 24.9 mmol) was dissolved in dry THF (100 mL) and cooled to 0 °C. *n*-Butyl lithium (10.2 mL, 2.5 M in hexane, 26 mmol) was added and the solution turned red. After 5 minutes, methyl iodide (1.55 mL, 24.9 mmol) was added and the mixture stirred at 0 °C for 1 hour while the solution turned yellow. *n*-Butyl lithium (10.5 mL, 2.5 M in hexane, 26 mmol) was added to the yellow solution which turned red and after 5 minutes freshly distilled (R)-isopropylideneglyceraldehyde (**5.20**) (3.427 g, 26.3 mmol) dissolved in dry THF (5.0 mL) was added and the reaction mixture was allowed to stir for 1 hour. The reaction was quenched with saturated aqueous ammonium chloride, and diluted with ethyl acetate, washed with saturated aqueous ammonium chloride and $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated into a yellow oil. The mixture was dissolved in a 1:1 THF/$H_2O$ mixture (40 mL) and TFA (2.5 mL) is added. The reaction mixture was stirred at room temperature for 16 hours. The solvent was removed under reduced pressure. Column chromatography (EtOAc/heptane 2:1) followed by recrystallization from heptane afforded (2*R*)-1-(9-methyl-9*H*-fluoren-9-yl)propane-1,2,3-triol (**5.42**) (2.935 g, 10.86 mmol, 44%) as white crystals.

***R*$_f$** = 0.45 (EtOAc/heptane 3:1)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 7.81 – 7.65 (m, 3H), 7.49 – 7.27 (m, 5H), 4.00 (d, J = 1.7 Hz, 1H), 3.27 (dd, J = 11.4, 6.9 Hz, 1H), 3.17 (dd, J = 11.4, 3.9 Hz, 1H), 2.91 – 2.81 (m, 1H), 2.17 (bs, 3H), 1.64 (s, 3H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 149.2, 148.5, 140.4, 140.2, 128.0, 127.9, 127.8, 127.6, 125.3, 123.2, 120.5, 120.5, 76.8, 69.8, 65.3, 54.6, 23.0

### 5.4.9 Preparation of 1-*C*-(9-methyl-9*H*-fluoren-9-yl)-2,3;5,6-di-*O*-isopropylidene-mannitol

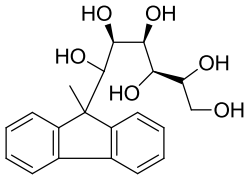



Fluorene (**5.38**) (2.500 g, 15.04 mmol) was dissolved in dry THF (50 mL) and cooled to 0 °C. *n*-Butyl lithium (6.0 mL, 2.5 M in hexane, 15 mmol) was added and the solution turned red. After 5 minutes, methyl iodide (0.93 mL, 15 mmol) was added and the mixture stirred at 0 °C for 1 hour while the solution turned yellow. *n*-Butyl lithium (6.0 mL, 2.5 M in hexane, 15 mmol) was added to the yellow solution which turned red and after 5 minutes 2,3;5;6-di-*O*-isopropylidene-α-D-mannose (**5.21**) (1.90 g, 7.30 mmol) was added and the reaction mixture was allowed to stir for 1 hour. The reaction was quenched with saturated aqueous ammonium chloride, and diluted with ethyl acetate, washed with saturated aqueous ammonium chloride and $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated into a yellow oil. Column chromatography (EtOAc/heptane 1:4) afforded the product 1-*C*-(9-methyl-9*H*-fluoren-9-yl)-2,3;5,6-di-*O*-isopropylidenemannitol (2.19 g, 4.97 mmol, 66%) as a white solid.

$R_f$ = 0.33 (EtOAc/heptane 1:2)

**$^1$H NMR:** $\delta_H$ (300 MHz, DMSO-d6): 7.93 – 7.71 (m, 2H), 7.71 – 7.51 (m, 2H), 7.48 – 7.15 (m, 4H), 5.42 (d, J = 4.8 Hz, 1H), 5.30 (d, J = 4.6 Hz, 1H), 4.07 (d, J = 4.8 Hz, 1H), 4.00 – 3.72 (m, 4H), 3.61 – 3.49 (m, 2H), 1.53 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.20 (s, 3H), 0.88 (s, 3H)

### 5.4.10 Preparation of 1-*C*-(9-methyl-9*H*-fluoren-9-yl)-mannitol (5.43)




1-*C*-(9-Methyl-9H-fluoren-9-yl)-2,3;5,6-di-*O*-isopropylidene-D-mannitol (326 mg, 0.747 mmol) was dissolved in a 1:1 THF/$H_2O$ mixture (4.0 mL) and TFA (0.25 mL) was added. The reaction mixture was stirred at room temperature for 22 hours. The solvent was removed under reduced pressure. Recrystallization from 20% EtOAc in heptane afforded 1-*C*-(9-methyl-9*H*-fluoren-9-yl)-mannitol (**5.43**) (140 mg, 0.39 mmol, 52%) as white crystals.

### 5.4.11 General method for monitoring gas development

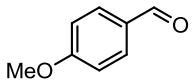
(2*R*)-1-(9-Methyl-9*H*-fluoren-9-yl)propane-1,2,3-triol (**5.44**) (136 mg, 0.50 mmol), $[Ir(coe)_2Cl]_2$ (11.6 mg, 0.013 mmol), rac-BINAP (16.1 mg, 0.026 mmol), LiCl (2.1 mg, 0.05 mmol) and diglyme (1.0 mL) were added to a Schlenk tube connected with a burette filled with water and stirred with reflux. The bottom of the burette was further connected to a water reservoir with a large surface area. The increase in volume was measured as a function of time.

### 5.4.12 General procedure for the two-chamber system reactions

In a two-chamber system, hexane-1,6-diol (118 mg, 1.00 mmol), $[Ir(cod)Cl]_2$ (16.8 mg, 0.025 mmol), rac-BINAP (31.0 mg, 0.050 mmol), LiCl (4.2 mg, 0.10 mmol) and mesitylene (2.0 mL, saturated with $H_2O$) were added to chamber one. To chamber two were added 4-bromoanisole (**5.52**) (125 µL, 1.00 mmol), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol), CataCXium A (19.7 mg, 0.055 mmol), TMEDA (0.30 mL, 2.00 mmol) and dry toluene (2.0 mL). The two-chamber system was flushed with argon. The system was sealed using a screw cap with a reflux condenser over chamber one and a screw cap over chamber two. Chamber one was heated to 170 °C while chamber two was heated to 80 °C. After 40 hours, the system was allowed to reach room temperature and the pressure was released upon opening of the system. The suspension in

chamber two was filtered through a silica plug and the filter cake was rinsed with ethyl acetate and the filtrate was concentrated. Column chromatography (1:9 $Et_2O$/pentane) produced 4-anisaldehyde (**5.53**) (97 mg, 0.71 mmol, 71%)

### *4-Anisaldehyde (5.51)*




***R*$_f$** = 0.25 ($Et_2O$/pentane 1:6)

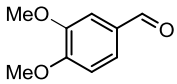
**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 9.88 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 191.0, 164.7, 132.1, 130.1, 114.4, 55.7

**MS:** *m/z* 136 [$M^+$]

NMR data are in accordance with literature values.[241]

### *3,4-Dimethoxybenzaldehyde*




***R*$_f$** = 0.28 ($Et_2O$/pentane 1:2)

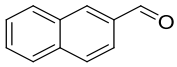
**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 9.80 (s, 1H), 7.41 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.36 (d, *J* = 1.8 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 190.9, 154.5, 149.6, 130.1, 126.9, 110.4, 108.9, 56.2, 56.0

**MS:** *m/z* 166 [$M^+$]

NMR data are in accordance with literature values.[248]

### *2-Naphthylaldehyde (5.11)*



***R*$_f$** = 0.28 ($Et_2O$/pentane 1:20)

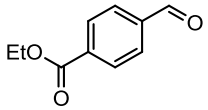
**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 10.17 (s, 1H), 8.35 (s, 1H), 8.07 – 7.86 (m, 4H), 7.68 – 7.56 (m, 2H).

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 192.4, 136.6, 134.7, 134.3, 132.8, 129.68, 129.27, 129.3, 128.2, 127.2, 122.9

**MS:** *m/z* 156 [$M^+$]

NMR data are in accordance with literature values.[241]

### *Ethyl 4-formylbenzoate*



***R*$_f$** = 0.20 ($Et_2O$/pentane 1:15)

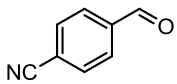
**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 10.09 (s, 1H), 8.19 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.1 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 4H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 191.8, 165.7, 139.2, 135.6, 130.3, 129.6, 61.7, 14.4

**MS:** *m/z* 178 [$M^+$]

NMR data are in accordance with literature values.[248]

### *4-Formylbenzonitrile*



***R*$_f$** = 0.44 ($Et_2O$/pentane 1:2)

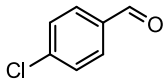
**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 10.09 (s, 1H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.85 (d, *J* = 8.3 Hz, 2H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 190.7, 138.9, 133.0, 130.0, 117.8, 117.7

**MS:** *m/z* 131 [$M^+$]

NMR data are in accordance with literature values.[241]

### *4-Chlorobenzaldehyde*



***R*$_f$** = 0.26 ($Et_2O$/pentane 1:30)

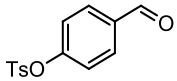
**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 9.99 (s, 1H), 7.88 – 7.73 (m, 2H), 7.57 – 7.45 (m, 2H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 191.0, 141.1, 134.9, 131.1, 129.6

**MS:** *m/z* 140 [$M^+$]

NMR data are in accordance with literature values.[241]

### *4-Formylphenyl 4-methylbenzenesulphonate*



***R*$_f$** = 0.29 ($Et_2O$/pentane 1:3)

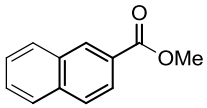
**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 9.97 (s, 1H), 7.86 – 7.80 (m, 2H), 7.77 – 7.68 (m, 2H), 7.33 (dd, *J* = 8.6, 0.6 Hz, 2H), 7.20 – 7.13 (m, 2H), 2.46 (s, 3H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 190.8, 154.02, 146.0, 135.0, 132.2, 131.4, 130.1, 128.6, 123.2, 21.9

**MS:** *m/z* 276 [$M^+$]

NMR data are in accordance with literature values.[248]

### *Methyl 2-naphthoate*



***R*$_f$** = 0.32 ($Et_2O$/pentane 1:40)

**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 8.62 (s, 1H), 8.07 (d, *J* = 8.6, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.69 – 7.50 (m, 2H), 3.99 (s, 3H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 167.4, 135.7, 132.6, 131.2, 129.5, 128.4, 128.3, 127.91, 127.5, 126.8, 125.4, 52.4

**MS:** *m/z* 186 [$M^+$]

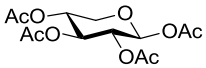
NMR data are in accordance with literature values.[262]

### 5.4.13 Reuse of iridium catalyst for the reductive carbonylation

Step 1: In a two-chamber system, $[Ir(cod)Cl]_2$ (16.8 mg, 0.025 mmol), rac-BINAP (31.0 mg, 0.050 mmol), LiCl (4.2 mg, 0.10 mmol) and mesitylene (2.0 mL, saturated with $H_2O$) were added to chamber one.

Step 2: To chamber one was added hexane-1,6-diol (118 mg, 1.00 mmol), and to chamber two were added 2-bromonaphthalene (**2.10**) (207 mg, 1.00 mmol), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol), CataCXium A (19.7 mg, 0.055 mmol), TMEDA (0.30 mL, 2.00 mmol) and dry toluene (2.0 mL). The two-chamber system was flushed with argon. The two chamber system was sealed using a screw cap with a reflux condenser over chamber one and a screw cap over chamber two. Chamber one was heated to 170 °C while chamber two was heated to 80 °C. After 40 hours, the system was allowed to reach room temperature and the pressure was released upon opening of the system. The two chamber system was under argon atmosphere during the following procedures. The suspension in chamber two was filtered through a silica plug and the filter cake was rinsed with toluene and a sample for GC analysis was taken out from and the yields were determined by using calibration curves. Chamber two was cleaned with toluene and step 2 was repeated.

### 5.4.14 Preparation of 1,2,3,4-tetra-*O*-acetyl-*β*-D-xylopyranose




To a suspension of D-xylose (4.981 g, 33.18 mmol) in dry $CH_2Cl_2$ (100 mL) was added $Et_3N$ (45.0 mL, 325 mmol) and the suspension was cooled to 0 °C. $Ac_2O$ (22.0 mL, 233 mmol) was added and after 30 minutes, the reaction was slowly allowed to reach room temperature. The suspension gradually turns into a dark solution and after 20 hours, the mixture was diluted with $CH_2Cl_2$. The organic phase was washed twice with aqueous 1 M HCl, saturated aqueous sodium bicarbonate and brine, dried with $MgSO_4$, filtered and concentrated into a red solid. Recrystallization from $CH_2Cl_2$/heptane afforded 1,2,3,4-tetra-*O*-acetyl-*β*-D-xylopyranose (7.238 g, 22.7 mmol, 69%)

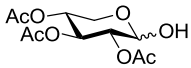
$\boldsymbol{R_f}$ = 0.49 (EtOAc/heptane 1:1)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$): 5.71 (d, *J* = 6.9 Hz, 1H), 5.20 (t, *J* = 8.3 Hz, 1H), 5.12 – 4.83 (m, 2H), 4.15 (dd, *J* = 12.0, 5.0 Hz, 1H), 3.52 (dd, *J* = 12.0, 8.4 Hz, 1H), 2.22 – 1.91 (m, 12H)

**$^{13}$C NMR:** $\delta_C$ (75 MHz, $CDCl_3$): 170.0, 169.5, 169.2, 92.2, 71.1, 69.6, 68.5, 63.0, 54.6, 21.0, 20.9, 20.8, 20.8

NMR data are in accordance with literature values.[263]

### 5.4.15 Preparation of 2,3,4-tri-*O*-acetyl-D-xylopyranose (5.61)




Following a procedure by Itoh *et al.* [264] A sodium methoxide (1.854 g, 34.3 mmol) suspension in dry THF (170 mL) was cooled to - 13 °C in a ice-NaCl bath. 1,2,3,4-Tetra-*O*-acetyl-*β*-D-xylopyranose (5.003 g, 15.7 mmol) was added. The brown solution slowly turns into a suspension and after 2 hours glacial acetic acid (3.1 mL, 54 mmol) was added. After stirring for 10 minutes the mixture was concentrated. The residue was dissolved in $CH_2Cl_2$ and washed with $H_2O$. The organic phase was dried with $MgSO_4$, filtered and concentrated. Column chromatography (EtOAc/heptane 1:1) afforded an anomeric mixture of 2,3,4-tri-*O*-acetyl-D-xylopyranose (**5.61**) (2.464 g, 8.92 mmol, 57%, ratio α/β 10:7) as a white solid together with recovered 1,2,3,4-tetra-*O*-acetyl-*β*-D-xylopyranose (0.855 g, 2.69 mmol, 17%)

Compound data as the α/β-mixture

***R*$_f$** = 0.22 (EtOAc/heptane 1:1)

**$^1$H NMR:** $\delta_H$ (400 MHz, $CDCl_3$): 5.51 (t, *J* = 9.6 Hz, 1H), 5.38 (t, *J* = 3.7 Hz, 1H), 5.23 (t, *J* = 9.2 Hz, 0.7H), 5.05 – 4.90 (m, 1.7H), 4.89 – 4.77 (m, 1.7H), 4.68 (dd, *J* = 8.5, 7.7 Hz, 0.7H), 4.13 (dd, *J* = 11.7, 5.5 Hz, 0.7H), 3.93 – 3.76 (m, 2H), 3.49 (d, *J* = 8.6 Hz, 0.7H), 3.37 (dd, *J* = 11.7, 9.9 Hz, 0.7H), 2.98 (dd, *J* = 3.9, 1.1 Hz, 1H), 2.12 – 2.07 (m, 5.1H), 2.07 – 1.99 (m, 10.2H)

**$^{13}$C NMR:** $\delta_C$ (100 MHz, $CDCl_3$): 171.1, 170.3, 170.19, 170.16, 170.0, 96.1, 90.5, 73.3, 71.5, 71.3, 69.4, 69.3, 69.2, 62.9, 58.7, 20.9, 20.8

$^1$H-NMR data are in accordance with literature values.[265]

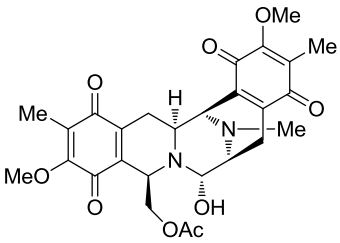
# Chapter 6: Towards the total synthesis of jorumycin

## 6.1 Background

The work performed in this chapter was performed in the group of Prof. Brian M. Stoltz at California Institute of Technology, Pasadena, CA, USA.

### 6.1.1 Jorumycin

The tetrahydroisoquinoline (THIQ) alkaloid family of antitumor antibiotics has been thoroughly studied over the last couple of decades. The studies commenced by the isolation of naphtyridinomycin by Kluepfel *et al.* in 1974.[266] The THIQs are particular interesting due to their complexity and remarkable biological activity as anticancer agents and antibiotics.[267] The extremely potent THIQ alkaloid, jorumycin (**6.01**) (Figure 41), inhibits growth of A549 human lung carcinoma and HT29 human colon carcina cell lines ($IC_{50}$ = 0.24 nm).[268–271] Jorumycin has been isolated from the mantle and mucous of the Pacific nudibranch sea slug *Jorunna funebris* in 2000 by Fontana *et al.*[268] The first total synthesis has been reported by Lane *et al.* in 2005,[269] followed by Wu and Zhu in 2009[270] and then Liu *et al.* in 2012.[271]



(-) jorumycin (**6.01**)

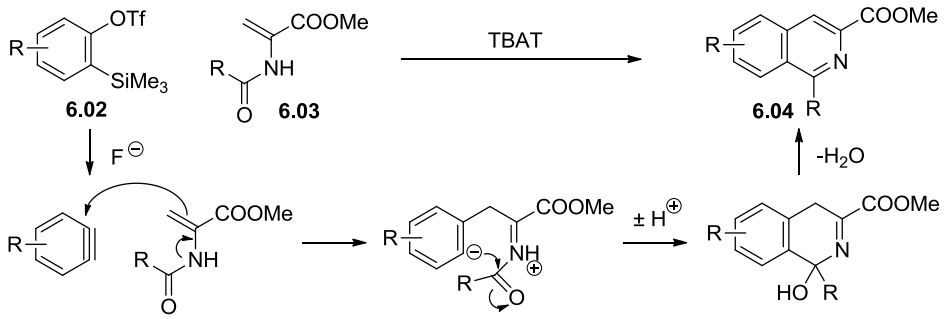
**Figure 41 - Structure of jorumycin**

### 6.1.2 Aryne annulation

The structure of benzyne has first been proposed by Roberts *et al.* in 1953 and the highly reactive intermediate has been exploited by synthetic organic chemists in the field of total synthesis.[272] Initially, the scope of the synthetic application has found somewhat limited as harsh conditions (e.g. strong base or high temperatures) are required to generate the aryne. The interest has been renewed as milder methods

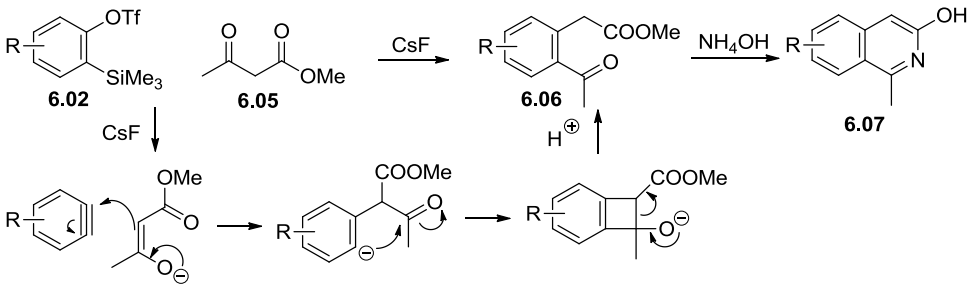
have been developed. By using *ortho*-silyl aryl triflates as precursors it is possible to prepare the reactive intermediate under almost neutral conditions.[273]

The proposed mechanism for the aryne annulation with benzyne and an acyl enamide is initiated by the fluorine activation of **6.02** forming the benzyne (Scheme 65). Conjugate nucleophilic addition from the enamide **6.03** forms the first carbon-carbon bond while the generated carbanion performs a nucleophilic attack on the amide. Overall, the condensation generates the aromatized isoquinoline structure **6.04**.



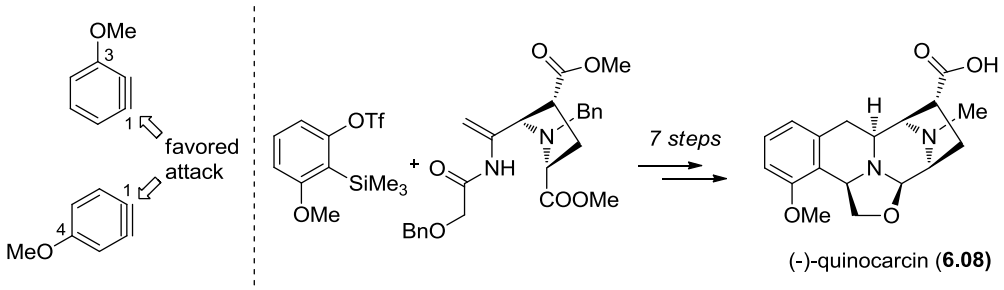

**Scheme 65 - Aryne annulation of benzynes and acyl enamides**

The proposed mechanism for the aryne annulation with benzyne and methyl acetoacetate (**6.05**) forms two new σ-bonds in a 4-membered ring (Scheme 66). Fragmentation completes the acyl-alkylation reaction and the product **6.06** can be converted into 3-hydroxyisoquinoline **6.07** by treatment with aqueous ammonia.



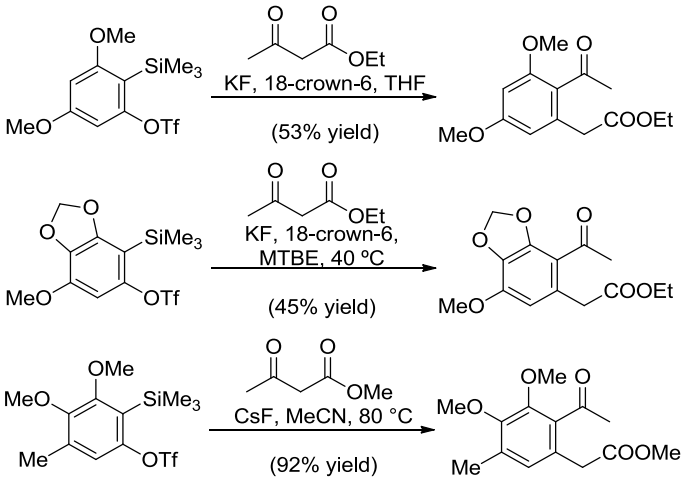

**Scheme 66 - Aryne annulation of benzynes and methyl acetoacetate**

The regioselectivity of these reactions are governed by the substituents on the aryne ring relative to the reactive triple bond. The electronic properties of the 3-methoxy-substituted arynes direct the nucleophilic attack to occur on C(1) (Scheme 67). This was applied to the total synthesis of (-)-quinocarcin (**6.08**).[274] Similarly the C(1) is favored for attack with 4-methoxysubstituted arynes.




**Scheme 67 – Regioselectivity in reactions of methoxysubstituted arynes**

In the case of polyalkoxy arynes, the closer o-alkoxy substituent completely directs the regioselective outcome as only one insertion product was formed (Scheme 68).[275]



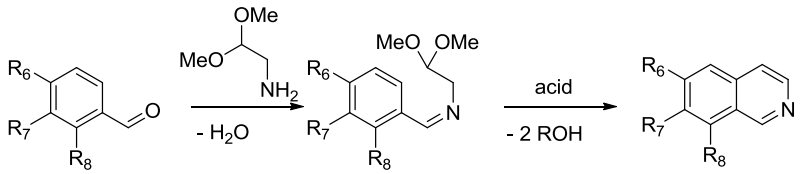

**Scheme 68 - Regioselectivity in polyalkoxy aryne annulations**

This regioselectivity of aryne annulations with polyalkoxides has been exploited in the total synthesis of several natural compounds like (-)-curvularin,[276] cercospera isolate,[275] phomopsin C and cytosporone B.[277]

### 6.1.3 Pomeranz-Fritsch cyclization

As an alternative approach to prepare isoquinolines, the Pomeranz-Fritsch cyclization is a method that has first been reported in the late 19th century independently by Pomeranz and Fritsch.[278,279] Prior to the benzyne methods, the Pomeranz-Fritsch reaction has been the only way to generate fully unsaturated isoquinolines **6.11**. The other methods where the Bischler-Napieralski cyclization which affords dihydroisoquinoline and the Pictet-Spengler ring closure which produces tetrahydroisoquinoline.[280,281] The reaction proceeds via cyclization of benzalaminoacetal intermediate **6.10** under highly acidic conditions. The benzalaminoacetal can be prepared by condensing a benzaldehyde **6.09** with an aminoacetal. Some examples are depicted in Table 31.

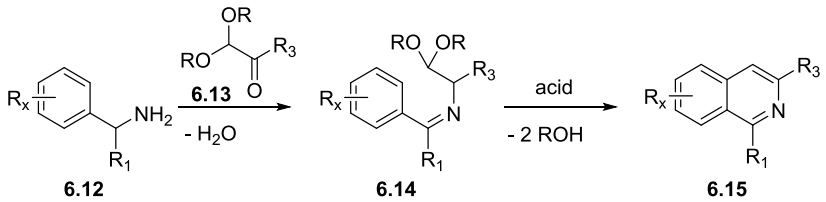
**Table 31 - Pomeranz-Fritsch cyclization**




**6.09** **6.10** **6.11**

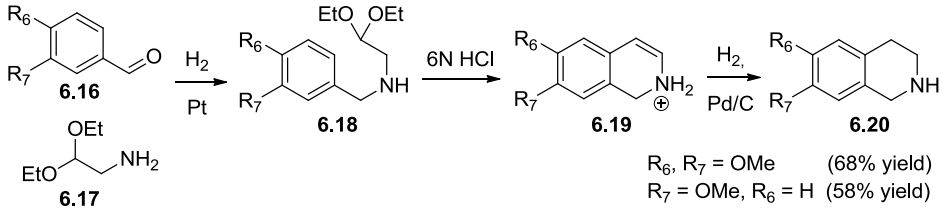
| Entry | Reagent | $R_6$ | $R_7$ | $R_8$ | yield |
|---|---|---|---|---|---|
| 1[282] | $H_2SO_4$ | H | Cl | Cl | 49% |
| 2[279] | $H_2SO_4$ | Cl | Cl | H | 9% |
| 3[283] | $BF_3$/AcOH | H | OMe | OMe | 23% |
| 4[281] | $BF_3$/AcOH + TFAA | H | OMe | OMe | 60-82% |
| 5[281] | $BF_3$/AcOH + TFAA | H | OMe | H | 73% |
| 6[284] | PPA | H | OMe | OMe | 6% |

In the Schlittler-Müller modification the Schiff base **6.14** is generated by condensing benzylamine **6.12** with glyoxal hemiacetal **6.13** and **6.14** can be cyclized into **6.15** under acidic conditions (Scheme 69).[285]



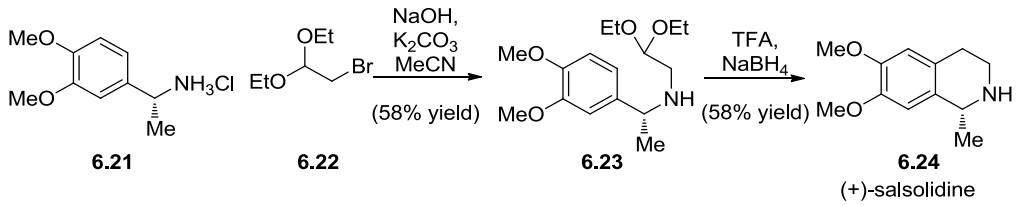

**Scheme 69 - Schlitter-Müller modification**

For the synthesis of THIQ's Bobbitt *et al.* have developed a modification of the Pomeranz-Fritsch cyclization (Scheme 70). Benzaldehyde **6.16** is condensed with aminoacetal **6.17** and the formed imine is reduced to the benzylaminoacetal **6.18**.[286] The cyclization of **6.18** is then performed by using 6 N HCl and the enamine **6.19** is further reduced producing the THIQ **6.20**.



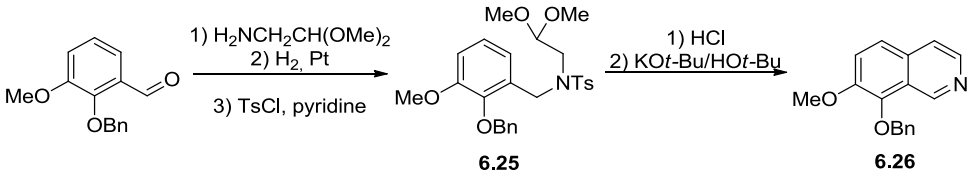

**Scheme 70 - Bobbitt modification**

Benzalaminoacetal **6.23** can also be prepared by alkylation of the benzyl amine **6.21** with bromoacetal **6.22**, which has been used for the synthesis of (+)-salsolidine **6.24** (Scheme 71).[287]




**Scheme 71 - THIQ formation**

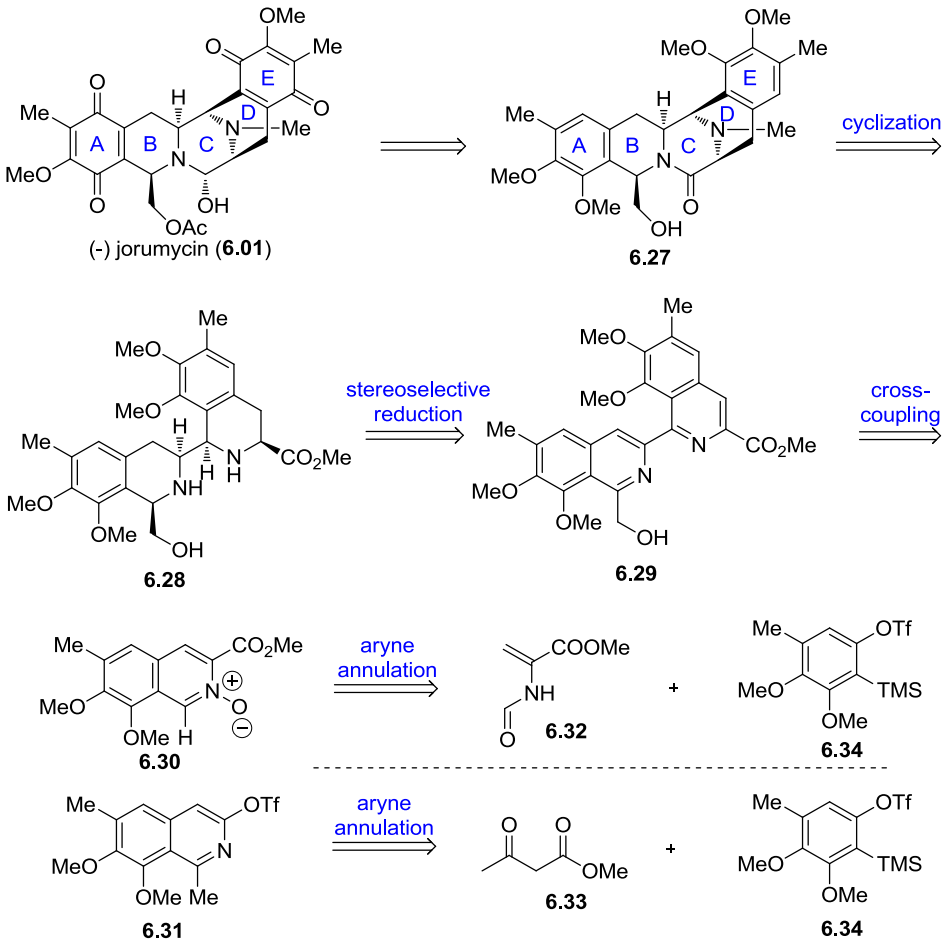
In the Jackson modification the amine is tosylated into **6.25** prior to the cyclization and the following elimination step provides the aromatization forming **6.26** (Scheme 72).[288–290]




**Scheme 72 - Jackson modification**

### 6.1.4 Retrosynthetic analysis

A retrosynthetic analysis was developed for the total synthesis of (-)-jorumycin (Scheme 73). Prior to the final manipulation for the approach, a late stage cyclization was needed for the generation of ring C in the pentacycle **6.27**. The precursor for the cyclization, the bis-THIQ **6.28**, could be formed by a reduction of bis-isoquinoline **6.29**. An enantioselective reduction method of the system needs to be developed. The bis-isoquinoline **6.29** can be assembled by the two distinct isoquinoline building blocks, **6.30** and **6.31** by a modification of the Fagnou cross-coupling.[291,292] The isoquinoline building blocks can be prepared by the aryne annulation reactions applying the same benzyne precursor **6.34**.

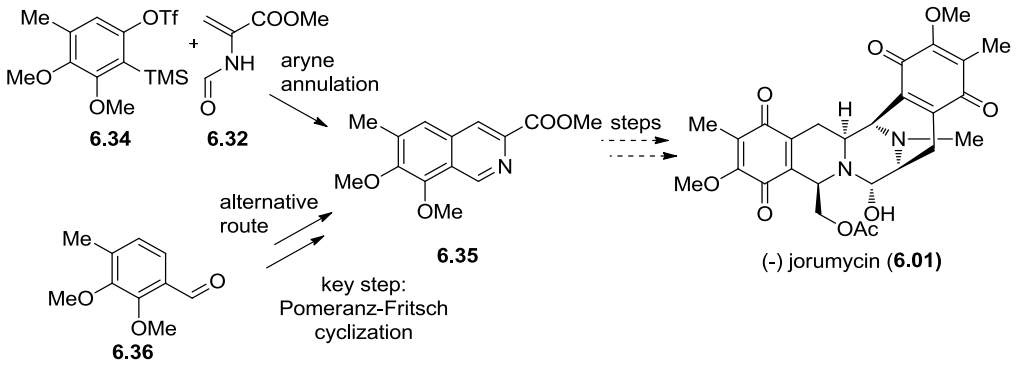



**Scheme 73 - Retrosynthetic analysis**

One major advantage of this strategy is the convergent approach. After the cross-coupling the entire carbon skeleton is assembled. Modification of the substituents on the isoquinoline scaffold introduces flexibility that makes the production of other natural or synthetic THIQ analogues readily available.

### 6.1.5 Project idea

The strategy involves isoquinoline **6.35** as a synthetic intermediate towards the synthesis of jorumycin (Scheme 74). At this point, the aryne annulation step for the formation of **6.35** only produces a 31% in a low a concentration 0.01M, and as a result this step needs optimization. Second, an alternative route for making **6.35** is desired involving the Pomeranz-Fritsch cyclization step (or a modification of such).

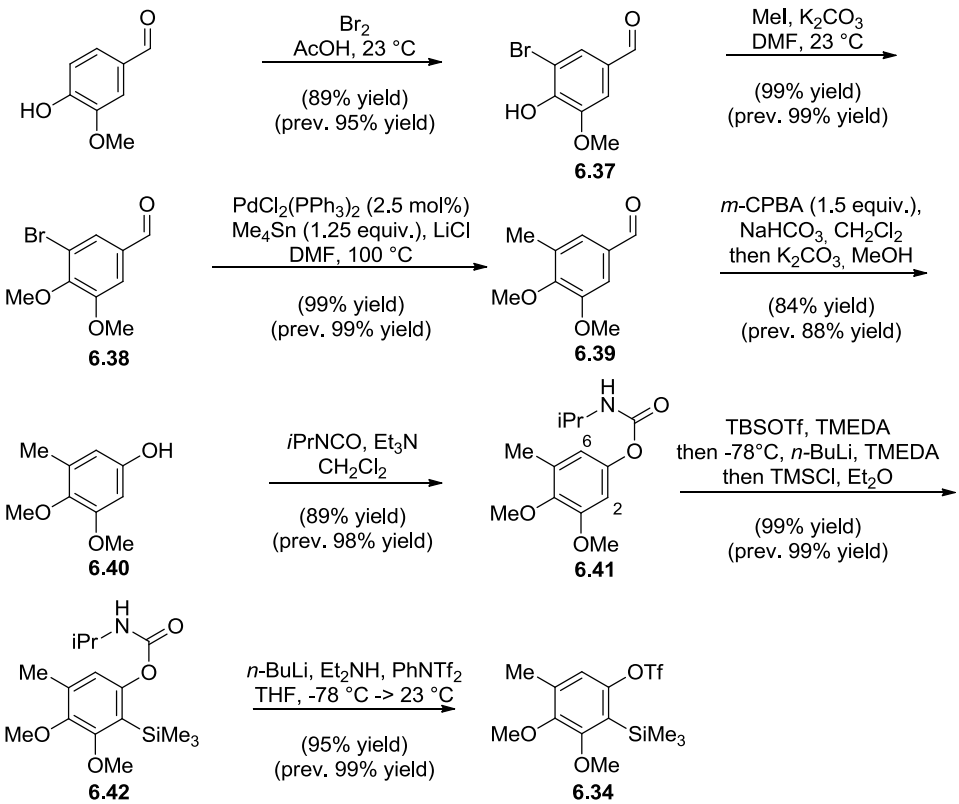



**Scheme 74 - Strategy for the total synthesis of (-)-jorumycin**

## 6.2 Results and discussion

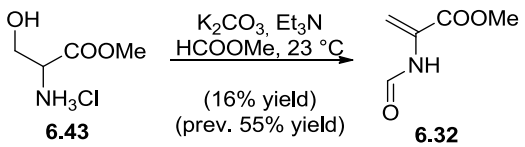
### 6.2.1 Aryne annulation route

Our first objective was to reproduce the preparation of the aryne precursor **6.34**. The steps were performed by using optimized procedures from Dr. Guillaume Lapointe, based on the published results group the group of Prof. Stoltz. [275] The yields obtained together with the previous yields are depicted in Scheme 75 and were satisfying. Bromination of vaniline provided the bromide **6.37** with complete regioselectively governed by the phenolic hydroxy group.[293] Methylating the bromide **6.37** under basic conditions furnished bromide **6.38** which underwent a palladium catalyzed Stille coupling with tetramethyltin which formed the product **6.39** in almost quantitative yield. A one-pot Baeyer-Villiger oxidation and cleavage of the resulting formate ester provided phenol **6.40** which should be stored under inert atmosphere to avoid oxidation to the corresponding quinone. For generating the *o*-silyl aryl triflate selectively a 3-step procedure developed by Bronner and Garg was followed.[294] The carbamate **6.41** was formed which was able to direct the silylation towards the C(2) position as **6.42** was produced with complete regioselectivity. Subsequent cleavage of the carbamate group in **6.42** and triflation of the obtained phenol furnished the aryne precursor **6.34**.




**Scheme 75 - Preparation of the aryne precursor 6.34**

The acyl enamine **6.32** was prepared starting from serine hydrochloride **6.43** following a procedure reported by Panella *et al.* although the yield of enamine **6.32** was not as high (Scheme 76).[295]

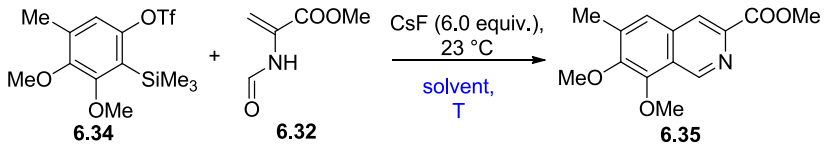



**Scheme 76 - Preparation of the acyl enamine 6.32**

The aryne annulation was a problematic step in the synthesis and so far the best yield of isoquinoline **6.35** was optimized to 31% on a 0.1 mmol scale using 6 equivalents of dry CsF in acetonitrile (Table 32, entry 1) and the yield drops on larger scale. A small solvent screening was performed and the best yield obtained was 35% using the same

conditions as previously optimized (Table 32, entry 2). Using THF, dioxane or toluene as solvent retarded the formation of isoquinoline **6.35** (Table 32, entry 3-5) and using an acetonitrile solvent mixture with either dioxane or toluene lowered the yield (Table 32, entry 6-7). Starting the reaction at - 16 °C and slowly increasing it to 23 °C did not result in a higher yield (Table 32, entry 8).

**Table 32 – Solvent effect**

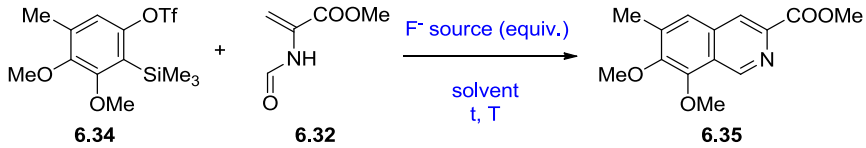



| Entry | solvent | T (h) | yield **6.35** |
|---|---|---|---|
| 1[a] | MeCN | 3 | 31% |
| 2 | MeCN | 3 | 35% |
| 3 | THF | 3 | traces |
| 4 | Toluene | 20 | 0% |
| 5 | Dioxane | 20 | 0% |
| 6 | 1:1 MeCN/Dioxane | 20 | 22% |
| 7 | 1:1 MeCN/toluene | 20 | 7% |
| 8[b] | MeCN | 6 | 32% |

a) Previous result. b) T = - 16 -> 23 °C.

Also a small fluoride source screening was performed in different solvents (Table 33). Employing 6 equivalents of tetra-*n*-butylammonium fluoride (TBAF) in THF resulted in a low yield of 23% (Table 33, entry 1). Acetonitrile as the solvent did not result in an apparent yield alteration compared to employing THF as the solvent (Table 33, entry 2-3). As the fluoride is a strong hydrogen bond acceptor it is almost impossible to dry hydrated samples of TBAF and therefore TBAF solutions in THF usually contain a substantial amount of $H_2O$.[296,297] Tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) was employed as a $H_2O$ free fluoride source equivalent to TBAF although no improvement was achieved in the aryne annulations reaction in toluene or THF (Table 33, entry 4-5).

**Table 33 – Source of F⁻**



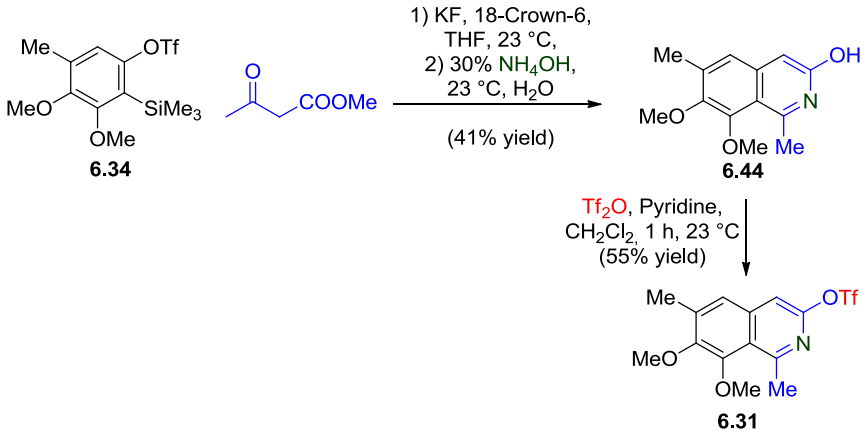

| Entry | solvent | $F^-$ (equiv.) | t (°C) | T (h) | yield **6.35** |
|---|---|---|---|---|---|
| 1 | THF | TBAF[a] (6.0) | 23 | 2 | 23% |
| 2 | THF | TBAF[a] (2.0) | 23 | 2 | 17% |
| 3 | MeCN | TBAF[a] (2.0) | 23 | 1 | 18% |
| 4 | Toluene | TBAT[a] (3.0) | 60 | 9 | 22% |
| 5 | THF | TBAT[a] (3.0) | 60 | 4 | 17% |

a) Structures shown in Figure 42


**Figure 42 - Structures of TBAF and TBAT**

Full conversion of **6.34** was observed and besides isoquinoline **6.35**, no other products were detected by NMR spectroscopy and UHPLC analysis and therefore further optimization of the reaction was complicated to perform because we did not know what side reactions we should suppress. At this point, no improvement could be made and the best conditions were those previously described.

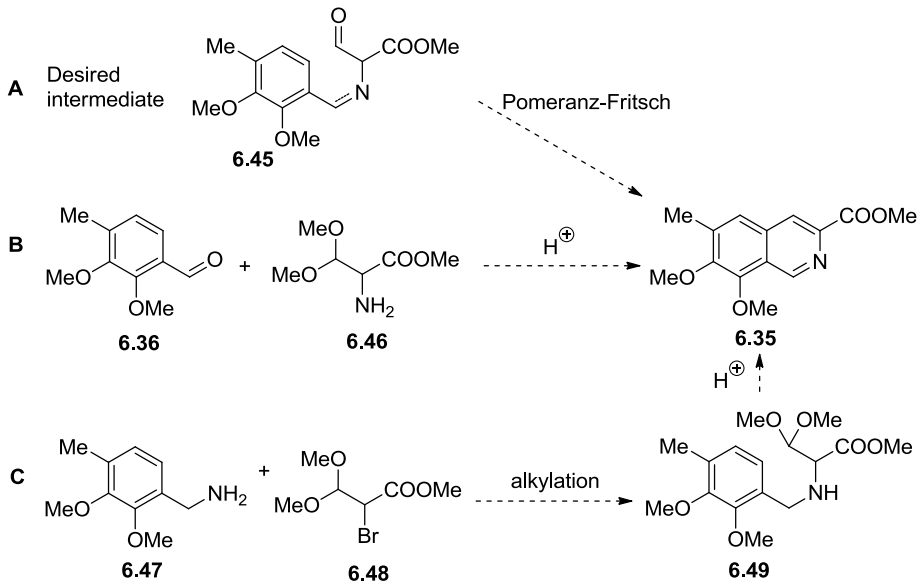
The second isoquinoline fragment **6.31** was synthesized in 3 steps from the aryne precursor **6.34** (Scheme 77). A one-pot procedure was initiated with an aryne annulation of precursor **6.34** with methyl acetoacetate and subsequently the intermediate acyl-alkylated product was converted into hydroxyisoquinoline **6.44** by treatment with aqueous ammonia. Triflation of hydroxyisoquinoline **6.44** formed the second isoquinoline fragment **6.31**.




**Scheme 77 - Preparation of the second isoquinoline fragment**

### 6.2.2 Strategy for bulk preparation of isoquinoline

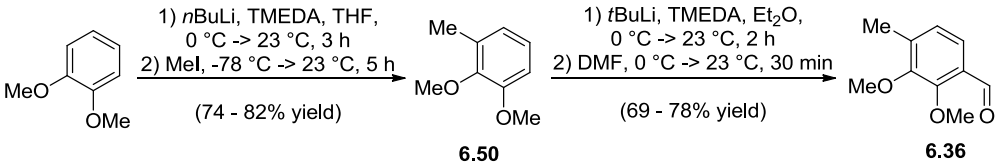
Since it was troublesome to get a significant amount of isoquinoline **6.35**, a more efficient and easy scalable method was needed. We thought that the Pomeranz-Fritsch cyclization via intermediate **6.45** would address the scale-up issue (Scheme 78, A). The cyclization to prepare **6.35** may be achieved from mixing benzaldehyde **6.36** with aminoacetal **6.46** (Scheme 78, B). Alternatively, benzylamine **6.47** can be alkylated with bromide **6.48** forming compound **6.49**, which also can perform the cyclization into **6.35** (Scheme 78, C).




**Scheme 78 - Strategies for the Pomeranz-Fritsch cyclization**

### 6.2.3 Starting material preparation

Benzaldehyde **6.36** was prepared over 2 steps from veratrole as reported by Werle *et al.* (Scheme 79).[298] TMEDA activates *n*BuLi by reorganizing the *n*BuLi hexamer in the hydrocarbon solution into a *n*BuLi tetramer, thereby making lithiation of the benzene ring possible.[299–301] The formed aryl lithium readily reacts with methyl iodide and the methyl group is regioselectively attached next to the methoxy groups in the product **6.50**. Compound **6.50** was lithiated again and the reaction of the aryl lithium species with DMF regioselectively furnished benzaldehyde **6.36**.



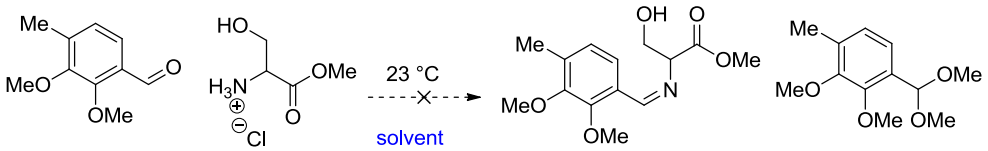

**Scheme 79 - Preparation of starting material**

Starting from benzaldehyde **6.36**, several approaches were investigated. Each of them will be described separately.

### 6.2.4 Schiff's base approach

In the Schiff's base approach, the initial goal was formation of the imine **6.51** which could potentially be converted in to the isoquinoline **6.35** in a few steps. In experiments with triethylamine, benzaldehyde **6.36** and methyl serine hydrochloride **6.43** in $CH_2Cl_2$ or methanol, the Schiff's base **6.51** were not isolated but starting benzaldehyde **6.36** was recovered (Table 34, entry 1-3). Without the addition of a base, the corresponding dimethoxy acetal **6.52** was formed as the major product. Also, heating the reaction mixture at reflux using a Dean Stark condenser did not produce any **6.51**. Further experiments using the Schiff's base approach were not performed and the focus was switched to the next strategy.

**Table 34 – Schiff's base approach**



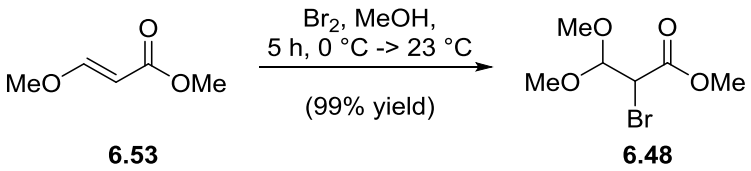

**6.36** **6.43** **6.51** **6.52**

| Entry | equiv. **6.43** | solvent | Base (equiv.) | Drying agent | T (h) | results |
|---|---|---|---|---|---|---|
| 1 | 1.4 | $CH_2Cl_2$ | $Et_3N$ (1.5) | $MgSO_4$ | 17 | No reaction |
| 2 | 1.5 | $CH_2Cl_2$ | $Et_3N$ (1.5) | MS 3A | 20 | No reaction |
| 3 | 1.5 | MeOH | $Et_3N$ (1.5) | MS 3A | 3 | No reaction |
| 4 | 2.0 | MeOH | - | MS 3A | 12 | **6.51** major |
| 5[a] | 1.5 | Toluene | $NaHCO_3$ (0.9) | Dean Stark | 3 | No reaction |

a) Heated at reflux

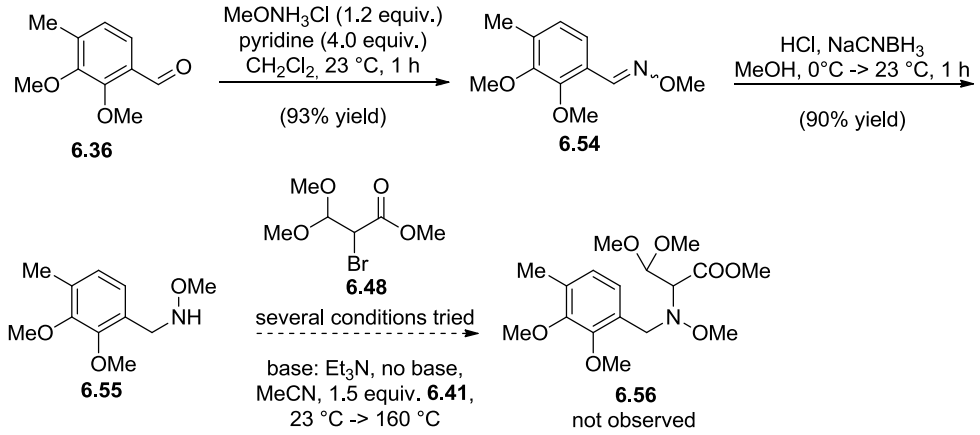
### 6.2.5 Methoxylamine approach

Bromide **6.48** was prepared in excellent yield starting from methyl trans-3-methoxyacrylate **6.53** and by using either bromine or NBS as brominating agent (Scheme 80).[302]




**Scheme 80 - Preparation of bromide 6.48**

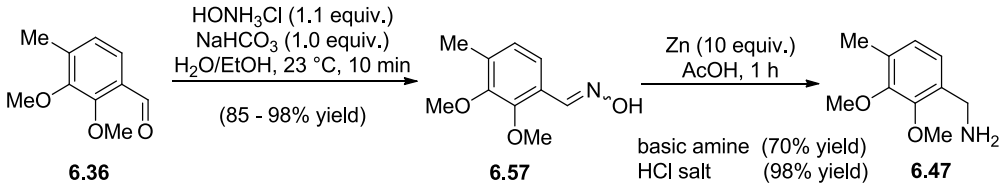
Methoxylamine **6.55** was obtained in two steps from benzaldehyde **6.36**, via methoxime **6.54**, in good yields (Scheme 81). Because of the alpha effect, the nitrogen in methoxylamine **6.55** might be nucleophilic enough to perform a substitution on bromide **6.48**. Several experiments to perform the substitution reaction with methoxylamine **6.55** on bromide **6.48** did not produce any of compound **6.56**, even after 2 hours of microwave heating at 160 °C and addition of $Et_3N$. The methoxylamine approach was not further investigated.




**Scheme 81 - Methoxylamine approach**

## 6.2.6 Benzylamine approach

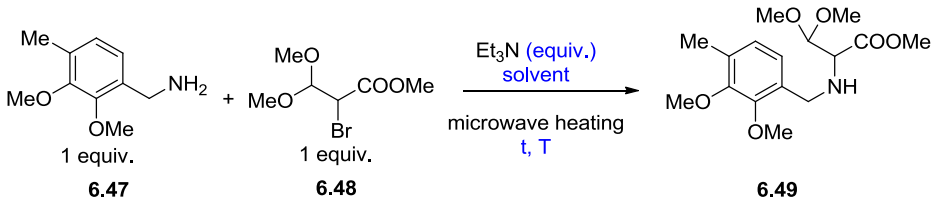
We then turned our focus on the preparation of benzylamine **6.47**. The benzaldehyde **6.36** was rapidly converted into the benzyl oxime **6.57** as a fine white solid in almost quantitative yield (Scheme 82). The reduction of the benzyl oxime **6.57** to benzylamine **6.47** was achieved using zinc powder in acetic acid, affording **6.47** both as the free base in 70% yield or as its HCl salt in 98% yield (Scheme 82).




**Scheme 82 - Preparation of benzylamine 6.47**

Benzylamine **6.47** could undergo substitution with bromide **6.48** under basic conditions. The product was unstable on silica gel and it was therefore not isolated, but the crude mixture was used directly for the cyclization step. Optimization conditions for the substitution reaction forming **6.49** are depicted in Table 35.

**Table 35 – Alkylation**




| Entry | equiv. $Et_3N$ | Solvent ([**6.41**]) | t (°C) | T (h) | results |
|---|---|---|---|---|---|
| 1 | 1.0 | MeCN (0.25 M) | 160 | 2 | **6.49** major |
| 2 | - | MeCN (0.25 M) | 160 | 1 | **6.49** not formed, messy |
| 3[a] | - | MeCN (0.25 M) | 160 | 1 | **6.49** major, messy |
| 4 | 2.0 | MeCN (0.25 M) | 150 | 1 | **6.49** major |
| 5 | 2.0 | MeCN (0.50 M) | 140 | 1 | **6.49** major |
| 6[b] | 2.0 | MeCN (0.50 M) | 80 | 36 | **6.49** minor, SM **6.47** left |
| 7[c] | 2.0 | MeCN (1.0 M) | 140 | 1 | **6.49** major, SM **6.47** left |
| 8[b] | 2.0 | DMF (1.0 M) | 110 | 12 | **6.49** major product, messy |
| 9[b] | 2.0 | Dioxane (1.0 M) | 100 | 12 | **6.49** major product |

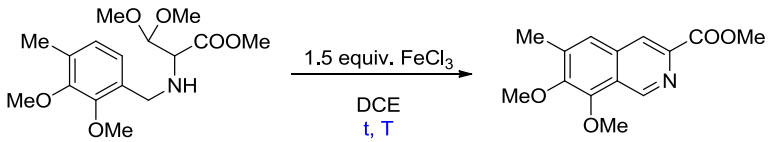
a) 0.5 equiv. of **6.40** used. b) Heating with oil bath. c) 11 mmol scale.

So far, our best conditions involved heating the reaction by microwave irradiation at 140 °C for 1 hour in acetonitrile (Table 35, entry 1-5). The addition of a base was necessary as the the reaction became impure without the addition of triethyl amine.

The use of other bases than triethyl amine was not pursued due to time limitations. Increasing the concentration of the reactants in the mixture resulted in an incomplete conversion of the benzylamine starting material **6.47**. Subjecting the reaction to conventional heating in DMF at 110 °C or dioxane at 100 °C also afforded the product **6.49** (Table 35, entry 8-9), although the reaction was not as clean as the reaction by microwave irradiation at 140 °C. Even though the use of microwave irradiation was limited in terms of scalability, larger amount of **6.49** could be obtained via successive experiments.

Through screening of different acids to perform the cyclization reaction on **6.49** we found that perfoming the reaction in either neat TFA or iron (III) chloride in 1,2-dichloroethane (DCE) resulted in the formation of isoquinoline **6.35**. Optimization of the iron (III) chloride promoted cyclization reaction is shown in Table 36.

**Table 36 – Iron (III) chloride promoted cyclization**




**6.49** **6.35**

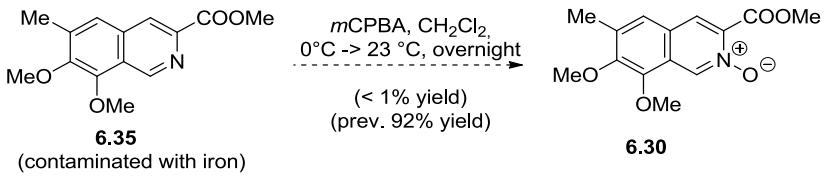
| entry | t (°C) | T (h) | Yields[a] **6.35** |
|---|---|---|---|
| 1 | Reflux | 68 | traces |
| 2[a] | 160 | 1 | 36% |
| 3[a,b] | 160 | 1 | traces |
| 4[c] | 120 | 8 | traces |

a) Two step yield from benzaldehyde **6.36**. a) Heated with microwaves. b) 0.1 equiv. $FeCl_3$. c) Heated in Schlenck tube

Conventional heating of the reaction mixture for 68 hours at reflux in DCE only produced trace amount of isoquinoline **6.35** (Table 36, entry 1)**.** Microwave irradiation allowed the temperature to be increased to 160 °C and after a reaction time of one hour isoquinoline **6.35** could be isolated in 36% yield over 3 steps on a 0.1 mmol scale (Table 36, entry 2). However, on a 12 mmol scale isoquinoline **6.35** could not be separated from iron contamination, even after several different work-up procedures

known to remove residual iron. $FeCl_3$ was not catalytically active in this transformation since lowering the amount of $FeCl_3$ from 1.5 equivalents to 0.1 equivalents only produced trace amounts of isoquinoline **6.35** (Table 36, entry 3).

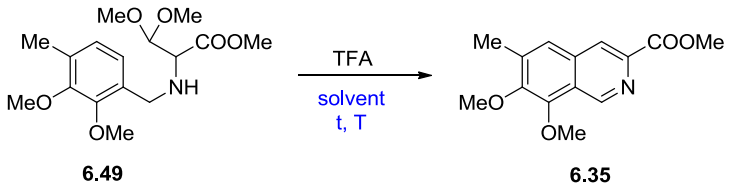
A major issue with the iron contamination was that the following oxidation step with *m*CPBA did not produce any isoquinoline *N*-oxide **6.30** although this transformation usually resulted in an excellent yield.




**Scheme 83 - Failed oxidation of isoquinoline 6.35**

As a consequence of the purification issues using $FeCl_3$ in the cyclization reaction, the TFA promoted cyclization reaction was optimized (Table 37).

**Table 37 – Cyclizations in TFA**

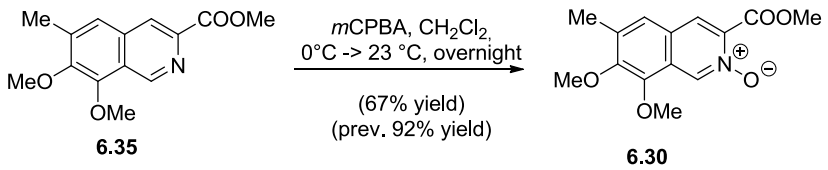



| entry | [H+] | Solvent | T (°C) | T (h) | Yields 6.35 |
|---|---|---|---|---|---|
| 1 | 2.6 M | CH2Cl2 | 23 | 15 | No reaction |
| 2[a] | conc. | - | 23 | 15 | No reaction |
| 3[a] | conc. | - | reflux | 35 | 29% |
| 4[a,b] | conc. | - | reflux | 41 | 35% |
| 5 | 1.3 M | DCE | reflux | 19 | No reaction |
| 6[c] | 1.3 M | DCE | reflux | 19 | No reaction |

a) TFA used as solvent. b) 1 equiv. 2-methoxypropene added. c) 1:1 TFA/TFAA mixture.

Isoquinoline **6.35** was produced by refluxing compound **6.49** in TFA for 35 hours in 29% yield. Addition of 2-methoxypropene raised the yield to 35% yield. A screening for acids besides TFA (TFAA, TFA/TFAA mixture, $H_2SO_4$, CSA, *p*TsOH, 2.0 M HCl in $H_2O$, 2.0 M HCl in MeOH, AcOH, $AlCl_3$, $TiCl_4$, hexafluoroisopropanol) showed no formation of isoquinoline **6.35**.

Gratifyingly, the *m*CPBA oxidation step to the isoquinoline *N*-oxide **6.30** now worked decently, affording 67% of the desired product (Scheme 84).




**Scheme 84 - Oxidation of isoquinoline 6.35**

## 6.3 Conclusion

The attempts to optimize the aryne annulation were not successful. Gratifyingly, the alternative route via a Pomeranz-Fritz cyclization produced some isoquinoline **6.35**, but some optimization was still necessary to obtain a higher output.

## 6.4 Experimental

### 6.4.1 General experimental

Unless otherwise stated, the reactions were performed under argon or nitrogen atmosphere. Solvents were dried by passage through an activated alumina column under argon. Amine bases were freshly distilled over $CaH_2$ prior to use. Reaction progress was monitored by thin-layer chromatography or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV or by staining with $KMnO_4$, *p*-anisaldehyde or 10% $H_2SO_4$ (aq.) and heated by heat gun until visible spots appeared. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40-63 nm) was used for column chromatography. $^1$H NMR spectra were recorded on a Varian Inova 500 MHz and Mercury Plus 300 NMR spectrometers and chemical shifts are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or $C_6HD_5$ (δ 7.16 ppm). $^{13}$C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and chemical shifts are reported relative to $CDCl_3$ (δ 77.16 ppm) or $C_6HD_5$ (δ 128.06 ppm). IR spectra were recorded by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption ($cm^{-1}$). High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in mixed ionization mode (MM: ESI-APCI+, electrospray ionization and atmospheric pressure chemical ionization). Reagents were purchased from Sigma-Aldrich, Acros, Organics, Strem or Alfa Aesar and used as received unless otherwise stated.

### 6.4.2 General procedure for the aryne annulation reactions

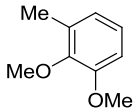
A flask was charged with CsF (91 mg, 0.6 mmol) and flame-dried under vacuum. 3,4-Dimethoxy-5-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**6.34**) (37.2 mg, 0.10 mmol) and methyl 2-formamidoacrylate (**6.32**) (38.7 mg, 0.30 mmol) in dry acetonitrile (10 mL) were added via syringe. After 3 hours at 23 °C, the red solution was quenched with aqueous HCl solution in $H_2O$. The phases were separated and the organic phase was washed with saturated aqueous $NaHCO_3$, dried with $Na_2SO_4$, filtered and concentrated. The product was purified by column chromatography (1:4 EtOAc/hexanes) yielding methyl 7,8-dimethoxy-6-methylisoquinoline-3-carboxylate (**6.35**) (9.0 mg, 0.035 mmol, 35%).

***R*$_f$** = 0.32 (1:1 EtOAc/hexanes)

**$^1$H NMR:** $\delta_H$ (500 MHz, $CDCl_3$) 9.51 (s, 1H), 8.44 (s, 1H), 7.52 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 4.01 (s, 3H), 2.48 (s, 3H)

**$^{13}$C NMR:** $\delta_C$ (125 MHz, $CDCl_3$) 166.7, 151.2, 147.7, 147.4, 141.1, 139.4, 132.9, 125.0, 124.3, 123.2, 61.8, 60.7, 53.0, 17.6

### 6.4.3 Methylation of Veratrole




To freshly distilled TMEDA (42.0 mL, 280 mmol) in dry THF (600 mL) was added veratrole (27.0 mL, 212 mmol). The solution was cooled to 0 °C. *n*-Butyl lithium (100 mL, 2.5 M in hexanes, 250 mmol) was added slowly and the clear solution turned into a yellow suspension. The reaction mixture was allowed to reach room temperature and stirred for 3 hours. The suspension was cooled to -78 °C and methyl iodide (15.6 mL, 251 mmol) was added slowly. The yellow color disappeared and the reaction mixture was allowed to reach 23 °C. After 4 hours the mixture was cooled to 0 °C and the reaction was neutralized with saturated aqueous ammonium chloride. The mixture was extracted 3 times with diethyl ether, dried with $MgSO_4$, filtered and concentrated. The product was purified by column chromatography (1:19 EtOAc/hexanes) yielding 1,2-dimethoxy-3-methylbenzene (**6.50**) (26.49 g, 174.0 mmol, 82%) as a colorless liquid.

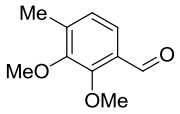
***R*$_f$** = 0.36 (1:19 EtOAc/hexanes)

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 6.95 (t, *J* = 7.9 Hz, 1H), 6.80 – 6.74 (m, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 2.28 (s, 3H).

**$^{13}$C NMR:** $\delta_C$ (125 MHz, $CDCl_3$) 152.8, 147.4, 132.1, 123.8, 122.9, 110.1, 60.2, 55.8, 15.9.

The data are consistent with previously reported data.[298]

### 6.4.4 Formylation of 1,2-dimethoxy-3-methylbenzene (6.36)




To freshly distilled TMEDA (45.4 mL, 302 mmol) in dry $Et_2O$ (600 mL) was added 1,2-dimethoxy-3-methylbenzene (**6.50**) (32.92 g, 216 mmol). The solution was cooled to 0 °C. *t*-Butyl lithium (152 mL, 1.7 M in pentanes, 259 mmol) was added by cannula over 30 minutes and the clear solution turned into a yellow suspension. The reaction mixture was allowed to reach 23 °C and stirred for 5 hours. The suspension was cooled to 0 °C and dry DMF (33.3 mL, 432 mmol) was added slowly. The yellow color disappeared and the reaction mixture was allowed to reach 23 °C. After 30 minutes, the reaction was neutralized with saturated aqueous ammonium chloride and the solution turned into a yellow suspension. The mixture was extracted 3 times with diethyl ether, washed with brine and $H_2O$, dried with $MgSO_4$, filtered and concentrated. The product was purified by column chromatography (1:40 to 1:20 EtOAc/hexanes) yielding 2,3-dimethoxy-4-methylbenzaldehyde (**6.36**) (26.85 g, 149 mmol, 69%) as a pale yellow liquid.

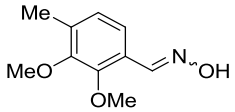
$\boldsymbol{R_f}$ = 0.22 (1:19 EtOAc/hexanes)

**$^1$H NMR:** $\delta_H$ (500 MHz, $CDCl_3$) 10.32 (s, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.05 – 6.91 (m, 1H), 3.98 (s, 3H), 3.85 (s, 3H), 2.31 (s, 3H).

**$^{13}$C NMR:** $\delta_C$ (125 MHz, $CDCl_3$) 189.8, 156.3, 140.6, 128.5, 126.3, 124.7, 122.9, 62.2, 60.3, 16.6.

The data are consistent with previously reported data.[298]

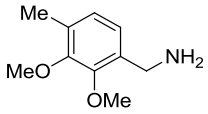
### 6.4.5 Oxime (6.57) formation from 2,3-dimethoxy-4-methylbenzaldehyde (6.36)




Sodium bicarbonate (12.52 g, 149 mmol) was dissolved in $H_2O$ (150 mL) and hydroxylamine hydrochloride (11.39 g, 164 mmol) was added slowly. A solution of 2,3-dimethoxy-4-methylbenzaldehyde (**6.36**) (26.85 g, 149 mmol) in ethanol (150 mL) was added. The solution was stirred at 23 °C for 10 minutes. The organic solvent was removed under reduced pressure. The aqueous layer was extracted 3 times with $CH_2Cl_2$, dried with $Na_2SO_4$, filtered and concentrated to yield pure 2,3-dimethoxy-4-methylbenzaldehyde oxime (**6.57**) (19.14g, 98 mmol, 98%) as a white solid. The cis/trans isomers were not separated.

***R*$_f$** (major) = 0.36 (1:4 EtOAc/hexanes)
**$^1$H NMR (major):** $\delta_H$ (500 MHz, $CDCl_3$) 8.13 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.28 (s, 3H).
**$^{13}$C NMR (major):** $\delta_C$ (125 MHz, $CDCl_3$) 152.0, 151.7, 146.6, 134.9, 126.3, 124.1, 121.2, 61.5, 60.3, 16.2.
$R_f$ (minor) = 0.22 (1:4 EtOAc/hexanes)
**$^1$H NMR (minor):** $\delta_H$ (500 MHz, $CDCl_3$) 8.13 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.28 (s, 3H).
**$^{13}$C NMR (minor):** $\delta_C$ (125 MHz, $CDCl_3$) 152.0, 151.7, 146.6, 134.9, 126.3, 124.1, 121.2, 61.5, 60.3, 16.2.
**IR:** $\nu_{max}$ (NaCl) 3428, 1637 $cm^{-1}$
**HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{10}H_{14}NO_3$ $[M+H]^+$: 196.0968; found 196.0977

### 6.4.6 Reduction of 2,3-dimethoxy-4-methylbenzaldehyde oxime (6.57)




2,3-Dimethoxy-4-methylbenzaldehyde oxime (**6.56**) (1.990 g, 10.2 mmol) was dissolved in glacial acetic acid (30 mL). Zinc dust (6.60 g, 102 mmol) was added to the stirrid mixture. After the addition, gas evolution was observed. The suspension was stirred at 60 °C for 1 hour. The mixture was slowly cooled to room temperature, filtered through Celite and the filter cake was rinsed with methanol. The filtrate was concentrated. The residue was diluted with $CH_2Cl_2$ and basified slowly with saturated aqueous sodium bicarbonate. The mixture was extracted 4 times with $CH_2Cl_2$, dried with $Na_2SO_4$, filtered and concentrated into the white solid, 2,3-dimethoxy-4-methylbenzyl amine (**6.47**) (1.270 g, 7.01 mmol, 70%). The compound was used without further purification.

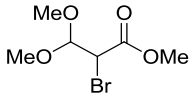
***R*$_f$** = 0.10 (1:10 MeOH/$CH_2Cl_2$)

**$^1$H NMR:** $\delta_H$ (500 MHz, $C_6D_6$) 6.88 (d, *J* = 7.7 Hz, 1H), 6.76 (d, *J* = 7.7, 1H), 3.79 (s, 2H), 3.64 (s, 3H), 3.58 (s, 3H), 2.41 – 2.34 (m, 2H), 2.18 (s, 3H).

**$^{13}$C NMR:** $\delta_C$ (125 MHz, $C_6D_6$) 151.8, 151.5, 134.9, 131.4, 125.9, 123.8, 60.3, 59.6, 41.85, 16.0.

**HRMS** (MM: ESI-APCI+) m/z calc'd for $C_{10}H_{16}NO_2$ $[M+H]^+$: 182.1176; found 182.1178

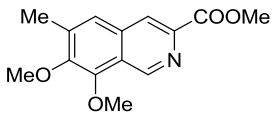
### 6.4.7 Preparation of methyl 2-bromo-3,3-dimethoxypropanoate (6.48)




Methyl trans-3-methoxyacrylate (**6.53**) (21.5 mL, 200 mmol) in methanol (500 mL) was cooled to 0 °C. Bromine (10.5 mL, 205 mmol) was added and the red solution was stirred for 5 hours while the reaction was allowed to reach 23 °C. Then the solvent was removed under reduced pressure. Saturated aqueous sodium bicarbonate was added, and the solution was extracted 3 times with $CH_2Cl_2$, dried with $Na_2SO_4$, filtered and concentrated. The yellow liquid (44.9 g) was used in the next step without further purification.

**$^1$H NMR:** $\delta_H$ (300 MHz, $CDCl_3$) 4.75 (d, *J* = 8.1 Hz, 1H), 4.24 (d, *J* = 8.1, 1H), 3.79 (s, 3H), 3.43 (s, 6H).
**$^{13}$C NMR:** $\delta_C$ (125 MHz, $CDCl_3$) 168.0, 103.4, 55.7, 53.9, 53.0, 43.7.

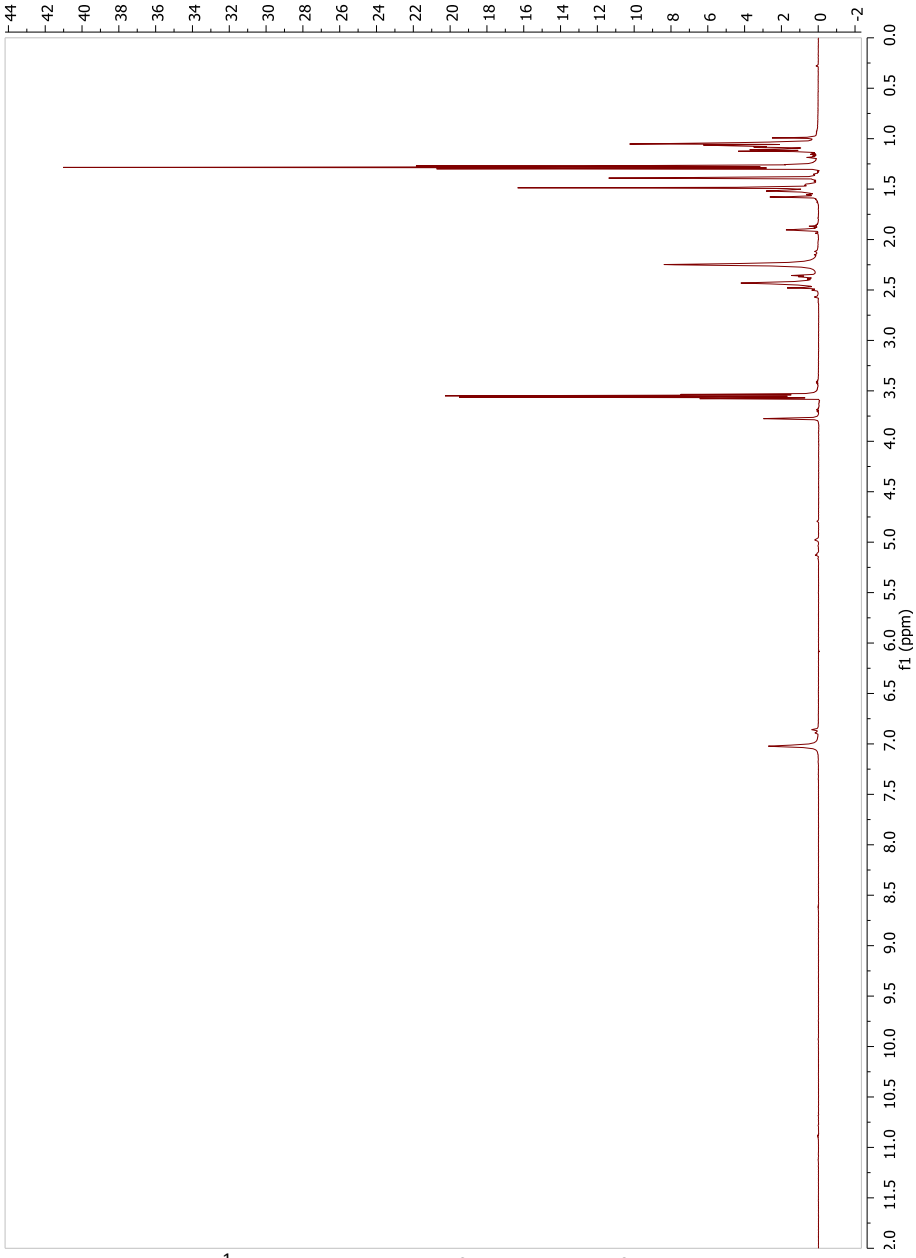
### 6.4.8 Two-step cyclization procedure for the formation of isoquinoline (6.35)



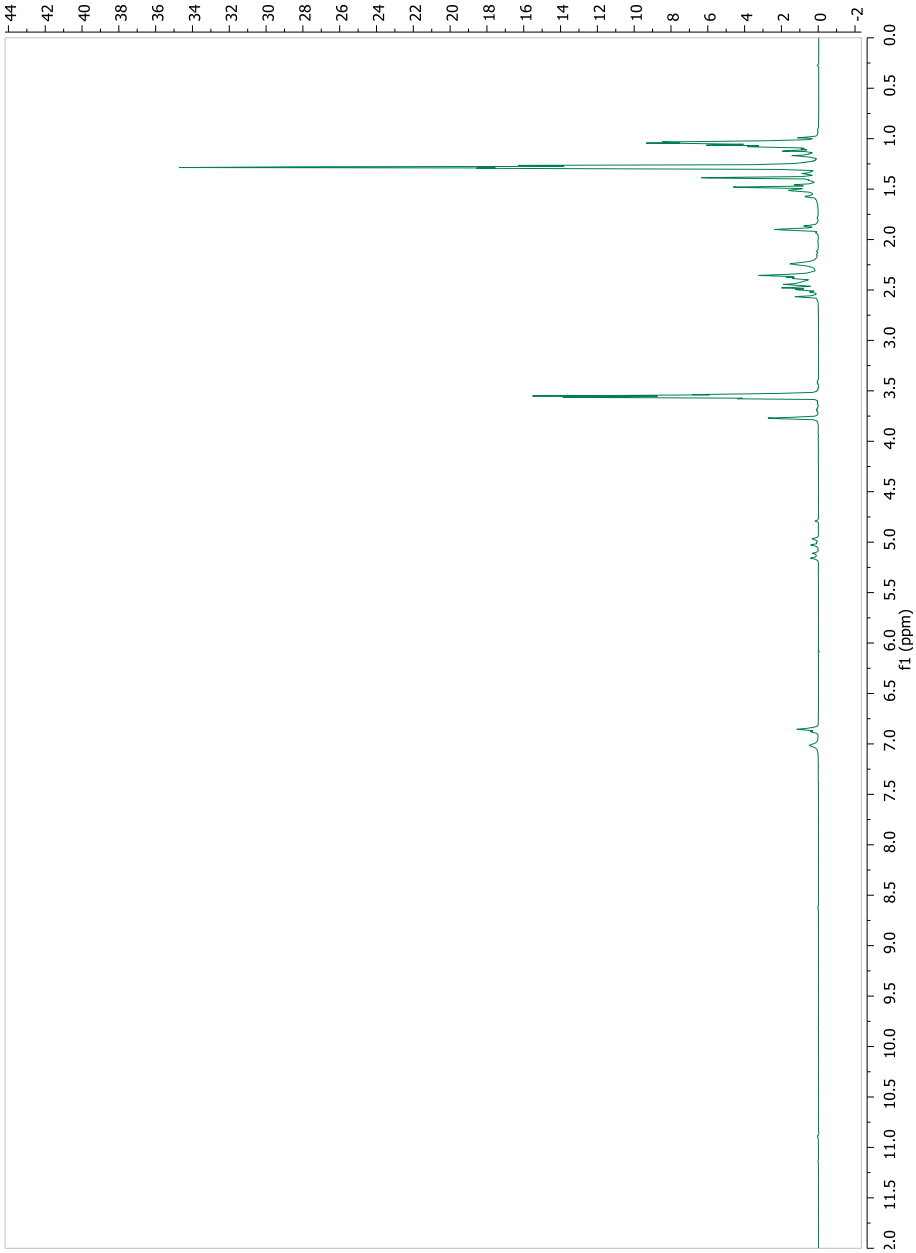

Crude methyl 2-bromo-3,3-dimethoxypropanoate (**6.41**) (114 mg, 0.5 mmol), 2,3-dimethoxy-4-methylbenzyl amine (**6.40**) (91 mg, 0.5 mmmol) and triethyl amine (0.14 mL, 1.0 mmol) were dissolved in acetonitrile (1.0 mL). The solution was heated for 1 hour at 140 °C by microwave irradiation. The red mixture was concentrated. The red residue was diluted with $CH_2Cl_2$ and washed with saturated aqueous sodium bicarbonate. The crude intermediate was extracted 3 times with $CH_2Cl_2$, dried with $Na_2SO_4$, filtered and concentrated into a red oil (158 mg).

To the red oil (65 mg) was slowly added TFA (0.5 mL). Some fumes were observed during the addition. The solution was further stirred at 75 °C for 35 hours. The dark red solution was concentrated into a red residue which was diluted with $CH_2Cl_2$ and basified with saturated aqueous sodium bicarbonate. The mixture was extracted 3 times with $CH_2Cl_2$, dried with $Na_2SO_4$, filtered and concentrated. The product was purified by column chromatography (1:4 ethyl acetate/hexanes) yielding methyl 7,8-dimethoxy-6-methylisoquinoline-3-carboxylate (**6.35**) (15 mg, 0.057 mmol, 29%)

# Appendix




Full $^{1}$H-NMR sprectrum from scan 1 of Figure 14




Full $^{1}$H-NMR sprectrum from scan 149 of Figure 14

# References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# The retro Grignard addition reaction revisited: the reversible addition of benzyl reagents to ketones

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ABSTRACT

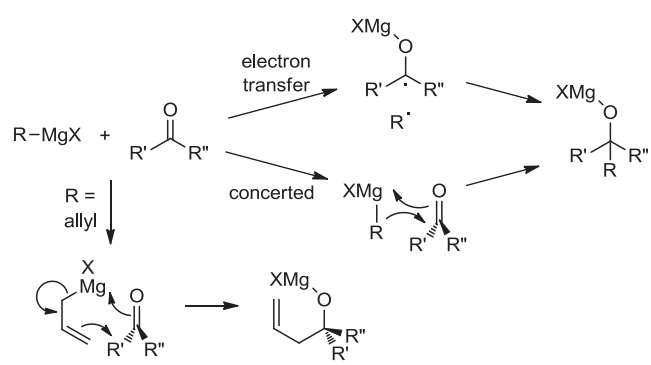
The Grignard addition reaction is known to be a reversible process with allylic reagents, but so far the reversibility has not been demonstrated with other alkylmagnesium halides. By using crossover experiments it has been established that the benzyl addition reaction is also a reversible transformation. The retro benzyl reaction was shown by the addition of benzylmagnesium chloride to di-*tert*-butyl ketone followed by exchange of both the benzyl and the ketone moiety with another substrate. Similar experiments were performed with phenylmagnesium bromide and *tert*-butylmagnesium chloride, but in these two cases the Grignard addition reaction did not show any sign of a reverse transformation.



## 1. Introduction

The addition of Grignard reagents to carbonyl compounds is one of the fundamental reactions in synthetic organic chemistry.[1] The transformation is highly favored since the two bonds formed (C–C and O–Mg) are much stronger than the two bonds broken (C–Mg and C=O). The mechanism has been thoroughly studied and it has been found that the reaction takes place by two rather different pathways depending on the nature of the reagent and the substrate (Scheme 1).[2] Electron transfer reactions are observed if the substrate is easily reduced by the acceptance of an electron and the reagent has an alkyl group, which may form a stabilized radical by donating an electron to the substrate. Steric hindrance is of little importance in this stepwise mechanism and the reactivity series for the Grignard reagents is often *tert*-butyl>isopropyl>*n*-butyl>ethyl>methyl.[2] If radical formation is not facilitated, the reaction takes place by a synchronous shift of the electron pairs. This four-centered concerted mechanism is highly dependent on steric factors since the electron shifts require a close approach of the reacting atoms. The reactivity series is often phenyl>ethyl>*n*-butyl>isopropyl>>*tert*-butyl.[2]

Allylic Grignard reagents are special, since by electron donation they may form the highly stabilized allyl radical and therefore react very fast by electron transfer mechanisms.[3] At the same time




**Scheme 1.** Mechanism of Grignard addition reaction.

allylmagnesium halides are extremely well suited for reaction in a concerted way since the normal high steric requirements of the magnesium atom with its coordination sphere of solvent molecules may be circumvented by conjugate addition of the naked γ-carbon in a cyclic six-center mechanism (Scheme 1). The reactions of allylmagnesium halides with many substrates therefore have half lives in the microsecond range.[3] In fact, allylations are so fast that they may compete with protonations by water making it possible to achieve certain allylic Grignard additions in aqueous media.[4]

Due to the high reactivity of Grignard reagents the addition is commonly viewed as being irreversible. However, this is not always completely true. The first suggestion of a retro Grignard addition

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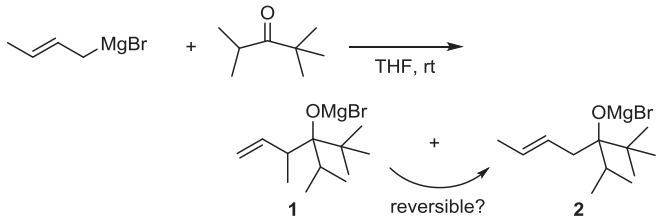
came from the observation that crotylmagnesium bromide, in the reaction with *tert*-butyl isopropyl ketone, gave the α-methallyl addition product **1** initially, while after a period of time the crotyl addition product **2** dominated (Scheme 2).[5]




**Scheme 2.** α-Methallyl versus crotyl adduct.

The process took place at room temperature and the result was interpreted as a rearrangement of the α-methallyl adduct **1** into the crotyl product **2**. The rearrangement was postulated to take place by allylic transposition of **1** into a *tert*-butyl isopropyl ketone–crotylmagnesium bromide complex, which then collapses through a four-centered transition state to the thermodynamically more stable crotyl product **2**.[5,6] However, it is unlikely that this rearrangement takes place by a true retro Grignard addition at ambient temperature. The heat of reaction for the addition of crotylmagnesium bromide to *tert*-butyl isopropyl ketone is 105 kJ/mol and the activation energy for the process is of the order of 30 kJ/mol.[7] The reverse reaction must then overcome a barrier of 135 kJ/mol and even with a favorable entropy of reaction, the reaction at room temperature would require hundreds of years, while the observed rearrangement occurs within a few hours.

That a retro Grignard addition is indeed possible was shown by another approach where two different crossover experiments were designed independently at the same time.[7,8] In the first, 1,3-dimethylallylmagnesium bromide was reacted with di-*tert*-butyl ketone and the initial adduct split into two batches and treated with *tert*-butyl isopropyl ketone and allylmagnesium bromide, respectively.[7] In both cases, significant allyl transfer occurred within an hour at 80 °C.[7] An essential requirement for this experiment is that both the added ketone and the Grignard reagent are more reactive than the original reactants, which makes the crossover a favorable transformation when the initial addition is a reversible reaction. In the second crossover experiment, two different Grignard adducts were mixed and heated to 65 °C.[8] The first was prepared from di-*tert*-butyl ketone and allylmagnesium bromide while the second was obtained from *tert*-butyl isopropyl ketone and crotylmagnesium bromide. Again, allyl crossover was observed indicating that the addition is reversible.[8]

The reversal process has found synthetic applications since sterically encumbered homoallylic tertiary alcohols have been used as allyl transfer reagents in the presence of various metals and bases.[9,10] First, the retro allylation transfers the allyl group to the metal, which is then followed by allylation of an aldehyde or an imine. This retro allylation/allylation sequence from homoallylic alcohols has been mediated by copper, gallium, and rhodium complexes at temperatures ranging from 25 to 130 °C.[9,10]

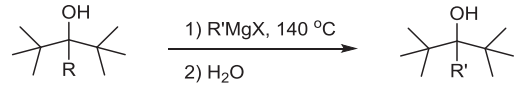
So far, however, the reversal has only been described with allylic substrates and no studies have been carried out with other Grignard reagents. Thus, the purpose of the present study is to investigate whether the reverse Grignard addition reaction is possible with other alkylmagnesium halides.

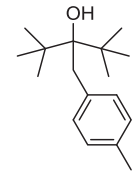
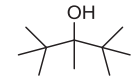
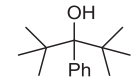
## 2. Results and discussion

The studies were performed by crossover experiments in line with the earlier work from one of us.[7] First, a concerted reaction was investigated where it is important that the Grignard reagents have little steric requirements and react rapidly with the carbonyl compounds. This is true for benzylic reagents, which are some of the most reactive Grignard reagents after the allylic compounds. In fact, the half life for the addition of benzylmagnesium bromide to acetone is about 5 ms,[3] while the same value for methylmagnesium bromide is around 0.2 s.[11] In the same way, the ketones should be sterically encumbered and non-enolizable in order to avoid protonation of the Grignard reagent. Therefore, benzyl Grignard and di-*tert*-butyl ketone were selected for the crossover experiments.

First, the exchange of Grignard reagent was investigated starting from 3-benzyl-2,2,4,4-tetramethylpentan-3-ol (Table 1). The tertiary alcohol was reacted with a large excess of the Grignard reagent, which immediately formed the corresponding alkoxide salt. The mixture was then heated in a sealed vial and the exchange monitored by GC. With *p*-methylbenzylmagnesium chloride no reaction occurred at 100 °C while a very low conversion was observed at 120 °C after 2 days. However, upon heating to 140 °C for 3 days the crossover product, 2,2,4,4-tetramethyl-(*p*-methylbenzyl) pentan-3-ol, was obtained in 51% yield after workup together with 48% of the starting alcohol (entry 1). Complete conversion was observed when the reaction was extended to 10 days where 77% yield of the exchange product was obtained (entry 2). This may indicate that the benzyl Grignard addition reaction is a reversible process although the temperature is significantly higher than for the corresponding allyl reagent.

**Table 1**
Retro Grignard by exchange of Grignard reagent




| Entry | R | R′MgX | Time (d) | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | Bn | *p*MeBnMgCl[b] | 3 |  | 51 |
| 2 | Bn | *p*MeBnMgCl[b] | 10 | | 77 |
| 3 | Bn | MeMgBr[c] | 6 |  | 75 |
| 4 | Bn | PhMgBr[d] | 10 |  | 7 |
| 5 | Ph | *p*MeBnMgCl[b] | 3 | — | 0 |
| 6 | Ph | MeMgBr[c] | 3 | — | 0 |

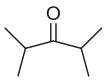
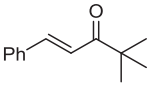
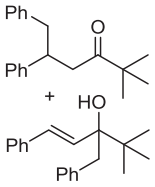
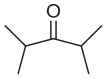
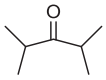
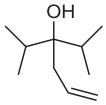
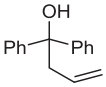
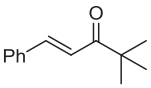
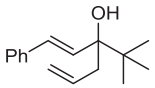
[a] Determined by GC.
[b] 0.67 M solution in THF.
[c] 3.0 M solution in $Et_2O$.
[d] 1.0 M solution in THF.

A similar crossover reaction was observed when the added Grignard reagent was changed to methyl- and phenylmagnesium bromide. With the former, the methyl addition product was generated in 75% yield after 6 days with some unreacted starting alcohol remaining (entry 3). With the latter, only 7% yield of the phenyl addition product was formed after 10 days, which may be due to the lower reactivity of phenylmagnesium bromide towards di-*tert*-butyl ketone (entry 4).[12] Attempts were also made to react 2,2,4,4-tetramethyl-3-phenylpentan-3-ol with Grignard reagents, but in this case no conversion was observed indicating that the phenyl Grignard addition reaction is not a reversible process at 140 °C (entries 5 and 6).

Thus, the benzyl group can be detached from a tertiary magnesium alkoxide, but in order to substantiate this as a retro Grignard addition reaction it is also important to trap the benzyl moiety with a ketone. Otherwise, the observed reaction could in principle be a result of alkoxide decomposition by a different mechanism. In fact, when the tertiary magnesium alkoxide was heated to 140 °C for 8 days in the absence of a Grignard reagent, di-*tert*-butyl ketone was formed in 62% yield. The driving force is the release of strain by converting the $sp^3$-hybridized alcoholate into the $sp^2$-hydridized ketone, but the pathway could potentially be different from a retro Grignard addition.

Therefore, the exchange of ketone was investigated next. The tertiary alcohol was treated with 1 equiv of methylmagnesium bromide to form the corresponding magnesium alkoxide, which was followed by addition of the ketone and heating to 140 °C (Table 2). No crossover occurred with diisopropyl ketone, which remained completely unreacted after 3 days (entry 1). However, with benzophenone the exchange product could be observed in 40% yield after the same period along with 60% of di-*tert*-butyl ketone (entry 2). A similar exchange was observed with benzalpinacolone, which afforded a mixture of the 1,4- and the 1,2-addition products in a combined 16% yield (entry 3). Together with the Grignard crossover experiment this verifies the reversibility of the benzylmagnesium bromide addition reaction at 140 °C. No exchange was observed when 2,2,4,4-tetramethyl-3-phenylpentan-3-ol was subjected to the same experiments, which again confirms the non-reversibility of the phenyl addition reaction (entries 4 and 5). For comparison, the corresponding allyl adduct was also included in the study since this particular crossover experiment has not previously been performed with the unsubstituted allyl moiety. As anticipated, the allyl exchange took place at a much lower temperature and in a shorter time than with the benzyl reagent and diisopropyl ketone, benzophenone, and benzalpinacolone could all be employed as the acceptor (entries 6–8).

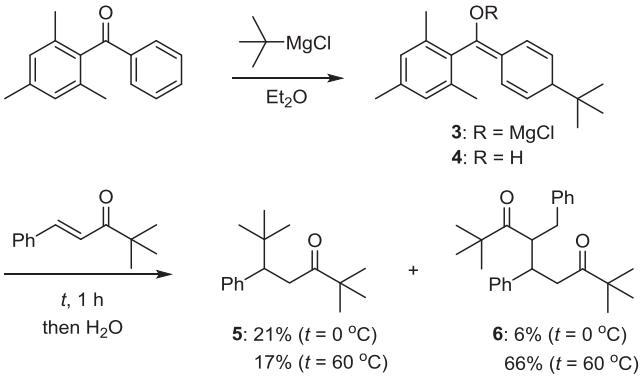
**Table 2**
Retro Grignard by exchange of ketone


| Entry | R | Ketone | Time (d) | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | Bn |  | 3 | — | 0 |
| 2 | Bn |  | 3 |  | 40 |
| 3 | Bn |  | 3 |  | 11+5 |
| 4 | Ph |  | 3 | — | 0 |
| 5 | Ph |  | 3 | — | 0 |
| 6[b] | Allyl |  | 0.75 |  | 34 |
| 7[b] | Allyl |  | 0.75 |  | 32 |
| 8[b] | Allyl |  | 0.75 |  | 50 |

[a] Determined by GC.
[b] Exchange performed at 70 °C.

Grignard additions by an electron transfer mechanism may also be reversible although this scenario is more complicated since two consecutive steps are involved. To simplify the picture *tert*-butylmagnesium chloride was selected in this case together with mesityl phenyl ketone and benzalpinacolone. Both ketones are known to react with *tert*-butylmagnesium chloride and afford only one product. Benzalpinacolone gives exclusively the 1,4-addition product in this case,[13] while mesityl phenyl ketone only furnishes the corresponding 1,6-adduct.[14] The latter is strained and lacks aromatic stabilization making it a good candidate for a reverse addition reaction.

Thus, a small excess of mesityl phenyl ketone was reacted with *tert*-butylmagnesium chloride at room temperature for 30 min to furnish the intermediate 1,6-adduct **3** (Scheme 3). The identity of this was confirmed by careful workup at 0 °C in the absence of air, which allowed the enol **4** to be characterized by NMR. Without workup the 1,6-adduct **3** was treated directly with 1 equiv of benzalpinacolone and the outcome of the subsequent reaction turned out to depend on the temperature. Upon additional stirring at 0 °C for 1 h the 1,4-addition product **5** was obtained in 21% yield together with 6% of diketone **6**. However, at 60 °C the ratio between the two products changed and diketone **6** was obtained in 66% yield along with 17% of **5**.

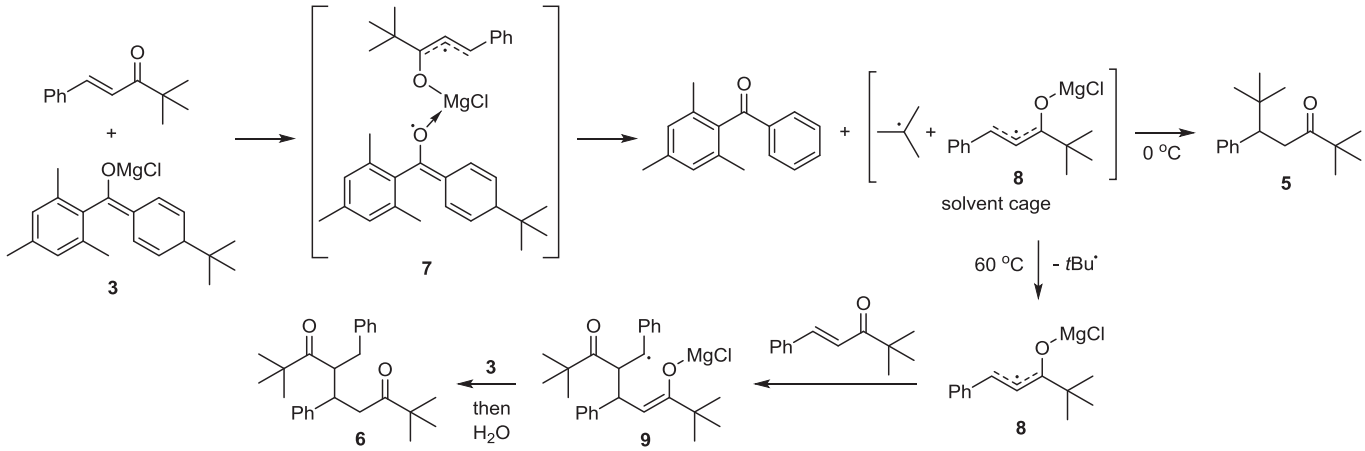



**Scheme 3.** Addition of *tert*-butyl Grignard.

These results were not due to unreacted *tert*-butylmagnesium chloride from the initial addition to mesityl phenyl ketone. This was confirmed by repeating the sequence with a significantly larger excess of mesityl phenyl ketone, which still produced a mixture of **5** and **6** after addition of benzalpinacolone. Hence, if the formation of these is caused by a retro Grignard addition reaction it should also be possible to perform a Grignard exchange experiment with adduct **3**. Therefore, *tert*-amylmagnesium chloride and allylmagnesium chloride were both allowed to react with **3**, but even after 3 days at 60 °C no exchange was observed at all in either of these two cases. This complete lack of reactivity came as a surprise since especially the highly reactive allylmagnesium chloride should capture even the slightest amount of mesityl phenyl ketone. Consequently, there appears to be no reversal of the *tert*-butyl Grignard addition reaction and the formation of products **5** and **6** in Scheme 3 must be due to a different pathway.

This pathway is believed to involve a slightly different electron transfer route than the classical *tert*-butyl Grignard addition

reaction (Scheme 4). Initially, benzalpinacolone coordinates to adduct **3** and then receives an electron to afford allyl radical **7**.[15] Mesityl phenyl ketone is regenerated by release of the *tert*-butyl radical into the solvent cage with allyl radical **8**.[16] At low temperature, these will combine to form **5** after workup. At higher temperature, however, allyl radical **8** can diffuse out of the cage and react with a second molecule of benzalpinacolone to form the new benzyl radical **9**,[17] which then accepts an electron from **3** to give **6** after workup.




**Scheme 4.** Mechanism for formation of ketones **5** and **6**.

In summary, we have demonstrated that the Grignard addition reaction is also a reversible process with benzylmagnesium halides. The reversibility was shown with a ketone, which becomes strained upon reaction with the Grignard reagent since this transformation is less exothermic and has a lower heat of activation than other Grignard addition reactions. On the other hand, the same reversibility was not observed with the less reactive phenyl- and *tert*-butylmagnesium halides.

## 3. Experimental section

### 3.1. General methods

Ketones were purchased from Sigma–Aldrich and used as received. Benzylic Grignard reagents were prepared in ampoules by slow addition of the benzylic halide to a magnesium suspension in freshly distilled THF under an argon atmosphere. The remaining Grignard reagents were purchased from Sigma–Aldrich and used as received. The base concentration was determined by quenching 1.0 mL of the solution in $H_2O$ followed by addition of a few drops of phenolphthalein and then titrating with nitric acid until a color shift from pink to colorless occurred.[18] THF was distilled from sodium and benzophenone while $Et_2O$ was dried over sodium. NMR spectra were recorded on a Varian Mercury 300 or a Bruker Ascend 400 spectrometer with residual solvent signals as reference. Melting points were measured on a Stuart SMP30 melting point apparatus and are uncorrected. Gas chromatography was performed on a Shimadzu QP5000 GC–MS instrument fitted with an Equity 5, 30 m×0.25 mm×0.25 μm column. High resolution mass spectra were recorded on an Agilent 1100 LC system, which was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with a lock mass probe.

### 3.2. General procedure for synthesis of tertiary alcohols

The ketone was dissolved in $Et_2O$ and a small excess of the Grignard solution in $Et_2O$ or THF was added under an argon atmosphere. The reaction was stirred overnight at room temperature. The mixture was diluted with $Et_2O$ and quenched with $H_2O$. The organic layer was separated and washed with saturated aqueous $NH_4Cl$ and $H_2O$. The organic phase was dried with $MgSO_4$, filtered, and concentrated. Further purification was performed either by vacuum distillation or by column chromatography (heptane/ethyl acetate or heptane/toluene).

### 3.3. General procedure for Grignard exchange reactions

3-Benzyl-2,2,4,4-tetramethylpentan-3-ol (65 mg, 0.28 mmol) was added to a 5 mL screw-top vial, which was flushed with argon. The Grignard solution (4.0 mL of 0.67 M *p*-methylbenzylmagnesium chloride in THF, or 4.0 mL of 1.0 M phenylmagnesium bromide in THF, or 2.5 mL of 3.0 M methylmagnesium bromide in $Et_2O$) was then added and the vial sealed. The solution was heated to 140 °C for the indicated time. The mixture was then allowed to reach room temperature and the reaction diluted with $Et_2O$ and quenched with $H_2O$. The organic layer was separated and washed with saturated aqueous $NH_4Cl$ and $H_2O$. Samples for GC analysis were taken out and yields were determined by using calibration curves with *n*-nonane as internal standard.

### 3.4. General procedure for ketone exchange reactions

The tertiary alcohol (0.34 mmol) was placed in a 5 mL screw-top vial, which was flushed with argon. $Et_2O$ (1.0 mL) and methylmagnesium bromide (0.11 mL, 3.0 mL in $Et_2O$, 0.33 mmol) were added. When the gas evolution had ceased the ketone (1.43 mmol) was added. The vial was sealed and heated to the indicated temperature for the time stated. Then the mixture was allowed to reach room temperature and the reaction was diluted with $Et_2O$ and quenched with $H_2O$. The organic layer was separated and washed with saturated aqueous $NH_4Cl$ and $H_2O$. A sample for GC analysis was taken out and yields were determined by using calibration curves with *n*-nonane as internal standard.

### 3.5. General procedure for *tert*-butyl exchange reactions

To mesityl phenyl ketone (525 mg, 2.34 mmol) in dry $Et_2O$ (10.0 mL) was added *tert*-butylmagnesium chloride (1.5 mL, 1.25 M in $Et_2O$, 1.90 mmol) under an argon atmosphere. The light brown suspension was stirred at room temperature for 30 min. The reaction was set to the indicated temperature and benzalpinacolone (358 mg, 1.90 mmol) was added. The reaction was stirred at this

temperature for 1 h. The mixture was diluted at room temperature with $Et_2O$ and quenched with $H_2O$. The organic layer was separated and washed with saturated aqueous $NH_4Cl$ and $H_2O$. The organic phase was dried with $MgSO_4$, filtered, and concentrated. A sample for GC analysis was taken out and yields were determined by using calibration curves with *n*-nonane as internal standard.

### 3.6. Di-*tert*-butyl ketone

3-Benzyl-2,2,4,4-tetramethylpentan-3-ol (68 mg, 0.29 mmol) was placed in a 5 mL screw-top vial, which was flushed with argon. $Et_2O$ (2.0 mL) and methylmagnesium bromide (0.09 mL of a 3.0 M solution in $Et_2O$, 0.27 mmol) were added. When the gas evolution had ceased the vial was sealed and heated to 140 °C for 8 days. The mixture was allowed to reach room temperature, diluted with $Et_2O$ and quenched with $H_2O$. The organic layer was separated and washed with saturated aqueous $NH_4Cl$ and $H_2O$. A sample for GC analysis was taken out and a yield of 62% was determined by using a calibration curve with *n*-nonane as internal standard.

### 3.7. 3-Benzyl-2,2,4,4-tetramethylpentan-3-ol (Table 1, entries 1–4)

$\delta_H$ (300 MHz, $CDCl_3$) 7.43–7.18 (m, 5H), 3.06 (s, 2H), 1.50 (s, 1H, OH), 1.17 (s, 18H); $\delta_C$ (75 MHz, $CDCl_3$) 139.8, 131.6, 128.0, 125.9, 80.0, 42.9, 38.5, 29.5; $\nu_{max}$ (film) 3598, 3085, 3061, 2959, 2916, 2878, 1493, 1481, 1452, 1393, 1086, 1001 $cm^{-1}$; HRMS (ESI) calcd for $C_{16}H_{26}O$ $[M+Na]^+$ *m/z* 257.1876, found 257.1875. $^1H$ NMR data are in accordance with literature values.[19]

### 3.8. 2,2,4,4-Tetramethyl-3-(*p*-methylbenzyl)pentan-3-ol (Table 1, entries 1 and 2)

$\delta_H$ (300 MHz, $CDCl_3$) 7.32 (d, *J*=8.0 Hz, 2H), 7.17 (d, *J*=8.0 Hz, 2H), 3.06 (s, 2H), 2.40 (s, 3H), 1.54 (s, 1H, OH), 1.21 (s, 18H); $\delta_C$ (75 MHz, $CDCl_3$) 136.4, 135.3, 131.4, 128.8, 79.8, 42.8, 38.0, 29.4, 21.3; HRMS (ESI) calcd for $C_{17}H_{28}O$ $[M+Na]^+$ *m/z* 271.2032, found 271.2032.

### 3.9. 2,2,3,4,4-Pentamethylpentan-3-ol (Table 1, entry 3)

Mp 39–41 °C, lit.[12] 39–41 °C; $\delta_H$ (300 MHz, $CDCl_3$) 1.26 (s, 1H, OH), 1.14 (s, 3H), 1.05 (s, 18H); $\delta_C$ (75 MHz, $CDCl_3$) 79.5, 41.1, 28.9, 21.7; $\nu_{max}$ (film) 3506, 2983, 2960, 2916, 2876, 1371, 1106, 1065 $cm^{-1}$. NMR data are in accordance with literature values.[20]

### 3.10. 2,2,4,4-Tetramethyl-3-phenylpentan-3-ol (Table 1, entry 4)

Bromobenzene (3.0 mL, 29 mmol) was added dropwise to a suspension of lithium metal (500 mg, 72 mmol) in dry $Et_2O$ (20 mL) under an argon atmosphere. The concentration was measured to 1.39 M by the phenolphthalein titration method.[18] The phenyllithium solution, thus obtained, was added dropwise to 2,2,4,4-tetramethylpentan-3-one (1.24 g, 8.7 mmol) under an argon atmosphere and stirred for 10 min. The mixture was diluted with $Et_2O$ and quenched with $H_2O$. The organic layer was separated and washed with saturated aqueous $NH_4Cl$ and $H_2O$. The organic phase was dried with $MgSO_4$, filtered, and concentrated. No further purification was needed. $\delta_H$ (300 MHz, $CDCl_3$) 7.77–7.72 (m, 1H), 7.64–7.58 (m, 1H), 7.41–7.33 (m, 1H), 7.29–7.23 (m, 2H), 1.98 (s, 1H, OH), 1.15 (s, 18H); $\delta_C$ (75 MHz, $CDCl_3$) 145.6, 128.0, 127.6, 127.4, 126.0, 125.8, 83.2, 41.7, 29.8; $\nu_{max}$ (film) 3624, 3057, 2961, 2913, 2877, 1483, 1392, 1370, 1053 $cm^{-1}$. NMR data are in accordance with literature values.[21]

### 3.11. 1,1,2-Triphenylethan-1-ol (Table 2, entry 2)

$\delta_H$ (300 MHz, $CDCl_3$) 6.95–7.45 (m, 13H), 6.95–6.89 (m, 2H), 3.56 (s, 2H), 2.23 (s, 1H, OH); $\delta_C$ (75 MHz, $CDCl_3$) 146.7, 135.9, 131.0, 128.2, 127.0, 126.9, 126.3, 78.0, 48.1; $\nu_{max}$ (film) 3548, 3086, 3060, 3027, 2956, 2910, 2856, 1492, 1446, 1199 $cm^{-1}$; HRMS (ESI) calcd for $C_{20}H_{18}O$ $[M-H_2O+H]^+$ *m/z* 257.1325, found 257.1325. NMR data are in accordance with literature values.[22]

### 3.12. 2,2-Dimethyl-5,6-diphenylhexan-3-one (Table 2, entry 3)

Mp 82–84 °C; $\delta_H$ (300 MHz, $CDCl_3$) 7.39–6.96 (m, 10H), 3.52 (quint, *J*=7.2 Hz, 1H), 3.02–2.81 (m, 3H), 2.74 (dd, *J*=17.2, 6.3 Hz, 1H), 1.00 (s, 9H); $\delta_C$ (75 MHz, $CDCl_3$) 214.4, 144.5, 140.1, 129.3, 128.4, 128.2, 127.8, 126.4, 126.1, 44.2, 42.7, 42.7, 42.6, 26.2; $\nu_{max}$ (neat) 3024, 2969, 2919, 1694, 1601, 1494, 1452, 1366, 1073 $cm^{-1}$; HRMS (ESI) calcd for $C_{20}H_{24}O$ $[M+H]^+$ *m/z* 281.1905, found 281.1905.

### 3.13. (*E*)-3-Benzyl-4,4-dimethyl-1-phenylpent-1-en-3-ol (Table 2, entry 3)

Mp 103–105 °C; $\delta_H$ (300 MHz, $CDCl_3$) 7.41–7.06 (m, 10H), 6.41 (d, *J*=16.0 Hz, 1H), 6.19 (d, *J*=16.0 Hz, 1H), 3.03 (d, *J*=13.1 Hz, 1H), 2.97 (d, *J*=13.0 Hz, 1H), 1.35 (s, 1H, OH), 1.09 (s, 9H); $\delta_C$ (75 MHz, $CDCl_3$) 137.5, 137.0, 134.0, 131.1, 129.6, 128.6, 128.2, 127.2, 126.7, 126.42, 79.2, 41.8, 38.4, 25.9; $\nu_{max}$ (neat) 3560, 3025, 2966, 2937, 2909, 2872, 1493, 1454, 1393, 1359, 1203, 1105, 1069, 1010 $cm^{-1}$; HRMS (ESI) calcd for $C_{20}H_{24}O$ $[M+H]^+$ *m/z* 281.1905, found 281.1900.

### 3.14. 3-Allyl-2,2,4,4-tetramethylpentan-3-ol (Table 2, entries 6–8)

$\delta_H$ (300 MHz, $CDCl_3$) 5.93 (ddt, *J*=17.5, 10.2, 7.5 Hz, 1H), 5.18–5.00 (m, 2H), 2.45 (d, *J*=7.5 Hz, 2H), 1.55 (s, 1H, OH), 1.05 (s, 18H); $\delta_C$ (75 MHz, $CDCl_3$) 137.4, 118.7, 78.9, 42.4, 38.0, 28.9; $\nu_{max}$ (film) 3581, 3076, 2960, 2918, 2878, 1482, 1392, 1370, 1001 $cm^{-1}$. NMR data are in accordance with literature values.[23]

### 3.15. 3-Allyl-2,4-dimethylpentan-3-ol (Table 2, entry 6)

$\delta_H$ (300 MHz, $CDCl_3$) 5.85 (ddt, *J*=17.5, 10.1, 7.4 Hz, 1H), 5.11–5.00 (m, 2H), 2.28 (dt, *J*=7.4, 1.3 Hz, 2H), 1.89 (sept, *J*=6.9 Hz, 2H), 1.26 (s, 1H, OH), 0.92 (d, *J*=6.9 Hz, 12H); $\delta_C$ (75 MHz, $CDCl_3$) 135.2, 117.7, 76.9, 38.4, 34.2, 17.6, 17.4; $\nu_{max}$ (film) 3500, 3077, 2964, 2880, 1468, 1385, 991 $cm^{-1}$; HRMS (ESI) calcd for $C_{10}H_{20}O$ $[M-H_2O+H]^+$ *m/z* 139.1481, found 139.1482. $^1H$ NMR data are in accordance with literature values.[24]

### 3.16. 1,1-Diphenylbut-3-en-1-ol (Table 2, entry 7)

$\delta_H$ (300 MHz, $CDCl_3$) 7.61–7.53 (m, 4H), 7.45–7.28 (m, 6H), 5.78 (ddt, *J*=17.2, 10.1, 7.2 Hz, 1H), 5.40–5.22 (m, 2H), 3.18 (d, *J*=7.2 Hz, 2H), 2.75 (s, 1H, OH); $\delta_C$ (75 MHz, $CDCl_3$) 146.5, 133.5, 128.2, 126.9, 126.0, 120.4, 76.9, 46.7; $\nu_{max}$ (film) 3554, 3475, 3059, 3025, 2978, 2923, 1493, 1446, 1345, 1166, 990 $cm^{-1}$. NMR data are in accordance with literature values.[23]

### 3.17. (*E*)-3-(*tert*-Butyl)-1-phenylhexa-1,5-dien-3-ol (Table 2, entry 8)

$\delta_H$ (300 MHz, $CDCl_3$) 7.16–7.46 (m, 5H), 6.58 (d, *J*=16.0 Hz, 1H), 6.35 (d, *J*=16.0 Hz, 1H), 5.89–5.67 (m, 1H), 5.20–5.17 (m, 1H), 5.16–5.12 (m, 1H), 2.66–2.51 (m, 1H), 2.40 (dd, *J*=13.5, 9.3 Hz, 1H), 1.74 (s, 1H, OH), 1.05–1.01 (m, 9H); $\delta_C$ (75 MHz, $CDCl_3$) 137.3, 134.6, 133.5, 129.5, 128.7, 127.3, 126.5, 119.7, 78.2, 40.1, 38.1, 25.7; $\nu_{max}$

(film) 3554, 3079, 3060, 3026, 2958, 2873, 975 $cm^{-1}$; HRMS (ESI) calcd for $C_{16}H_{22}O$ $[M-H_2O+H]^+$ *m/z* 213.1638, found 213.1638. NMR data are in accordance with literature values.[25]

### 3.18. (4-(*tert*-Butyl)cyclohexa-2,5-dien-1-ylidene)(mesityl) methanol (4)[14]

To mesityl phenyl ketone (222 mg, 0.99 mmol) in dry $Et_2O$ (10 mL) was added *tert*-butylmagensium chloride (1.0 mL of 1.25 M solution in $Et_2O$, 1.25 mmol) under an argon atmosphere. The light brown suspension was stirred at room temperature for 30 min. The mixture was quenched with an ice-cold solution of saturated aqueous $NH_4Cl$. The organic layer was removed with an air-tight syringe and washed inside the syringe with $H_2O$. The organic phase was transferred to a pear-shaped flask under argon followed by removal of the solvent by a flow of argon. The remaining colorless oil was dissolved in $CDCl_3$ and added to an NMR tube inside an argon-filled Schlenk flask. $\delta_H$ (400 MHz, $CDCl_3$) 6.90 (s, 2H), 6.83 (dt, *J*=10.3, 1.7 Hz, 1H), 5.86 (ddd, *J*=10.3, 4.4, 1.9 Hz, 1H), 5.64 (dt, *J*=10.3, 1.6 Hz, 1H), 5.54 (ddd, *J*=10.3, 4.2, 1.9 Hz, 1H), 4.01 (s, 1H), 2.80 (tt, *J*=4.3, 1.5 Hz, 1H), 2.21 (s, 3H), 2.16 (s, 3H), 2.11 (s, 3H), 0.84 (s, 9H); $\delta_C$ (100 MHz, $CDCl_3$) 144.4, 138.6, 137.8, 137.5, 132.7, 128.5, 128.4, 127.0, 125.4, 125.2, 122.0, 110.9, 48.9, 35.9, 27.4, 21.3, 19.62, 19.60.

### 3.19. 2,2,6,6-Tetramethyl-5-phenylheptan-3-one (5)

Following the general procedure for *tert*-butyl exchange, mesityl phenyl ketone and *tert*-butylmagnesium chloride were reacted at 0 °C for 1 h. After workup ketone **5** was purified by column chromatography (1:50 ethyl acetate/pentane) and recrystallization from toluene/methanol. Mp 99–100 °C, lit.[26] 100–101 °C; $\delta_H$ (300 MHz, $CDCl_3$) 7.25–7.10 (m, 5H), 3.09–3.15 (m, 2H), 2.71 (dt, *J*=10.8, 8.9, 8.9 Hz, 1H), 1.01 (s, 9H), 0.88 (s, 9H); $\delta_C$ (75 MHz, $CDCl_3$) 214.5, 143.0, 129.4, 127.6, 126.1, 50.4, 44.4, 37.9, 33.7, 28.4, 26.5; MS *m/z* 246 $[M^+]$; $\nu_{max}$ (neat) 2959, 2915, 2867, 1699, 1472, 1365, 1342 $cm^{-1}$. $^{13}C$ NMR data are in accordance with literature values.[27]

### 3.20. 4-Benzyl-2,2,8,8-tetramethyl-5-phenylnonane-3,7-dione (6)

Following the general procedure for *tert*-butyl exchange, mesityl phenyl ketone and *tert*-butylmagnesium chloride were reacted at 60 °C for 1 h. After workup diketone **6** was obtained as a 3:1 diastereomeric mixture, which were separated and purified by column chromatography (1:50 ethyl acetate/pentane and then 1:1 toluene/heptane) and recrystallization from heptane. For major diastereomer: Mp 94–95 °C; $\delta_H$ (300 MHz, $CDCl_3$) 7.07–7.35 (m, 8H), 6.90–6.93 (m, 2H), 3.76 (dt, *J*=6.7, 4.5 Hz, 1H), 3.44 (ddd, *J*=11.1, 4.5, 3.3 Hz, 1H), 3.11 (d, *J*=6.7 Hz, 2H), 2.94 (dd, *J*=12.6, 11.1 Hz, 1H), 2.71 (dd, *J*=12.6, 3.3 Hz, 1H), 1.10 (s, 9H), 0.74 (s, 9H); $\delta_C$ (75 MHz, $CDCl_3$) 217.2, 213.7, 143.5, 140.0, 129.4, 128.6, 128.3, 128.1, 126.8, 126.3, 54.0, 44.7, 44.2, 41.1, 35.9, 34.0, 26.6, 26.0; $\nu_{max}$ (neat) 3062, 3027, 2968, 1707, 1682, 1476, 1454, 1364 $cm^{-1}$; HRMS (ESI) calcd for $C_{26}H_{34}O_2$ $[M+Na]^+$ *m/z* 401.2451, found 401.2452; HRMS (ESI) calcd for $C_{26}H_{34}O_2$ $[M+H]^+$ *m/z* 379.2632, found 379.2633.

For minor diastereomer: $\delta_H$ (300 MHz, $CDCl_3$) 7.25–7.02 (m, 8H), 6.97–6.84 (m, 2H), 3.56 (ddd, *J*=9.1, 7.4, 5.1 Hz, 1H), 3.49–3.37 (ddd, *J*=10.0, 6.7, 3.4 Hz, 1H), 3.10 (dd, *J*=17.2, 10.0 Hz, 1H), 2.77–2.46 (m, 3H), 0.92 (s, 9H), 0.68 (s, 9H); $\delta_C$ (75 MHz, $CDCl_3$) 219.0, 213.2, 142.4, 139.6, 129.3, 128.5, 128.4, 128.4, 126.8, 126.5, 52.9, 44.8, 44.2, 43.4, 39.8, 38.2, 26.3, 26.2.

## Supplementary data

$^1H$ and $^{13}C$ NMR spectra of all compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.12.070.

## References and notes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